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Epidemiological situation of *Staphylococcus aureus* in Algeria

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Dedication

*To my mother, **Djamila**, the most precious being in my life, for guiding me and supporting me and most of all loving me unconditionally even when I thought all hope was lost, you are the moon of my life.*

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Abstract:

Staphylococcus aureus is both an animal and human opportunistic bacterium capable of causing a wide range of severe diseases. The emergence and dissemination, in the human and animal populations of strains of *Staphylococcus aureus* having acquired mechanisms of resistance to antibiotics, are becoming a worrying public and animal health problem, which is why *S. aureus* is on the World Health Organization (WHO) high priority list of priority antibiotic resistant pathogens.

On the basis of some twenty recent articles, we tried to develop an overall synthesis of the epidemiological situation of S aureus in Algeria, discussing the health risk and antibiotic resistance and the current surveillance system, and propose recommendations to be implemented on several levels. The second aim is to take stock of the national and international strategies initiated by, or involving, the "Veterinary Services Department" DSV as part of the surveillance of the health hazard linked to Staph aureus in Algeria.

Keywords : *Staphylococcus aureus*, MRSA, Antimicrobial Resistance, PVL, CA-MRSA, clone.

Résumé :

Staphylococcus aureus est une bactérie opportuniste animale et humaine capable de provoquer un large éventail de maladies graves. L'émergence et la dissémination, dans les populations humaines et animales de souches de *Staphylococcus aureus* ayant acquis des mécanismes de résistance aux antibiotiques, deviennent un problème préoccupant de santé publique et animale, c'est pourquoi *S. aureus* figure en bonne place dans l'Organisation mondiale de la santé (OMS), liste prioritaire des agents pathogènes prioritaires résistants aux antibiotiques.

Sur la base d'une vingtaine d'articles récents, nous avons tenté d'élaborer une synthèse globale de la situation épidémiologique du S aureus en Algérie, discutant du risque sanitaire et de la résistance aux antibiotiques et du système de surveillance actuel, et proposons des recommandations à mettre en œuvre à plusieurs niveaux. Le deuxième objectif est de faire le point sur les stratégies nationales et internationales initiées par ou impliquant la « Direction des Services Vétérinaires » DSV dans le cadre de la surveillance du risque sanitaire lié au Staph aureus en Algérie.

Mots clés : *Staphylococcus aureus*, SARM, Résistance aux antimicrobiens, PVL, CA-MRSA, clone.

الملخص:

المكورات العنقودية الذهبية هي بكتيريا انتهازية للإنسان والحيوان قادرة على التسبب في مجموعة واسعة من الأمراض الشديدة. ظهور وانتشار سلالات المكورات العنقودية الذهبية التي اكتسبت آليات مقاومة للمضادات الحيوية بين البشر والحيوانات، وأصبحت مشكلة مقلقة للصحة العامة والحيوانية. وهذا سبب تواجدها على قائمة منظمة الصحة العالمية (WHO) لمسببات الأمراض المقاومة للمضادات الحيوية ذات الأولوية

على أساس ما يقرب من عشرين مقالة حديثة، حاولنا تطوير توليفة شاملة للوضع الوبائي للمكورات العنقودية الذهبية في الجزائر، ومناقشة المخاطر الصحية ومقاومة المضادات الحيوية ونظام المراقبة الحالي، واقتراح توصيات ليتم تنفيذها على عدة مستويات. الهدف الثاني هو تقييم الاستراتيجيات الوطنية والدولية التي بدأتها أو تشارك فيها مديرية الخدمات البيطرية في إطار مراقبة المخاطر الصحية المرتبطة بالبكتيريا العنقودية الذهبية في الجزائر.

الكلمات المفتاحية:

المكورات العنقودية الذهبية، مقاومة المضادات الحيوية، المكورات العنقودية الذهبية المقاومة للميثيسيلين، استنساخ، بانتون فالنتين لوكوسيدين

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MRSA: Methicillin resistant S. aureus.
MSSA: Methicillin susceptible Staphylococcus aureus
DNA: Deoxyribonucleic acid.
RNA: Ribonucleic acid.
PVL: Panton-Valentine leucocidin.
CA-MRSA: Community-Associated methicillin resistant S. aureus.
HA-MRSA: Hospital-associated methicillin resistant S. aureus.
LA-MRSA: Livestock-Associated methicillin resistant S. aureus.
CC: Clonal complex.
PCR: Polymerase chain reaction.
SCCmec: Chromosomal staphylococcal cassette.
TSST-1: Toxic shock syndrome toxin.
VISA : Vancomycin intermediate S. aureus.
VRSA : Vancomycin resistant S. aureus.
P: Penicillin.
OX: Oxacillin.
FOX: Cefoxitin.
AMC: Amoxicillin + Clavulanic acid.
GM: Gentamicin.
E: Erythromycin.
K: Kanamycin.
TE : Tetracycline.
VA : Vancomycin.
CL : Clindamycin.
RIF: Rifampicin.
STX: Trimethoprim/Sulfamethoxazole.
S: Susceptible.
R: Resistant.
I: Intermediate.

Introduction:

Staphylococcus aureus is both an animal and human opportunistic bacterium. It is one of the most important pathogenic *Staphylococcus* species in veterinary medicine (Djoudi *et al*., 2015).

Its danger lies in its potential for transmission from animals to humans and vice-versa. It thus has a huge impact on animal health and welfare causing major economic losses in livestock production and on life expectancy. This zoonotic potential is now well recognized, with consideration that contact with animals is one of the most important factors influencing colonization and infection in human populations, as pets are now deemed reservoirs of Methicillin-Resistant Staphylococcus aureus (MRSA) (Andreoletti *et al.*, 2009).

The problem of antibiotic resistance in *S. aureus* has become the subject of preoccupation for the public, notably due to the rise of multidrug resistance with the spread of the methicillin-resistant strains (MRSA) in humans, farm animals and in the wider environment, which is a serious cause of concern for both human and veterinary medicine (Agabou *et al*., 2017).

Based on some twenty recent articles, we tried to develop an overall synthesis of the epidemiological situation of *Staphylococcus aureus* in Algeria. Discussing the health risk and antibiotic resistance, and evaluating the importance of S. aureus, and the health and economic threat it represents. In order to propose recommendations to be implemented on several levels.

The secondary purpose of our study is to take stock of the national and international strategies initiated by, or involving, the "Veterinary Services Department" (DSV) as part of the surveillance of the health hazard linked to Staph aureus in Algeria: programs involved in the antibiotic resistance and food safety.

1.1 Staphylococcus aureus:

1.2 Generalities on *Staphylococcus aureus:*

1.2.1 History:

Staphylococci were identified as cause of wound infection in 1881, by Scottish surgeon "Sir Alexander Ogston", in pus from a surgical abscess. Named *Staphylococcus* for the grape-like clusters observed under the microscope, "*Staphyle*" meaning grape in Greek and "Cocci" meaning grain or bay or egg (Ghanem, 2017).

In 1884, it was isolated by German scientist Anton Rosenbach. *S. aureus* (from *aurum* gold) was named "golden staph" for the golden colonies it grows on bacterial media, in opposition to the pale translucent colonies of *S. albus* (Khan, 2017).

1.2.2 Classification:

The classification of Staphylococci was made on the basis of the analysis of genes encoding ribosomal RNA (rRNA). Until the end of the 1990s, the genus *Staphylococcus* was classified within the group of *Micrococcaceae* with *Micrococcus* and *Stomatococcus*. Species of the genus Staphylococcus differ from those of the genus Micrococcus however, by their optional anaerobic metabolism, a G + C content of between 30 and 39% (against 63 and 73% for *Micrococcus*), and by their wall containing a peptidoglycan and acids teichoic (Euzéby, 1997).

The new classification of Staphylococci according to Euzeby in the Bergey's manuel 2002 and NCBI (National Center for Biotechnology Information), is:

- **Reign:** *Bacteria or Eubacteria.*
- **Phylum:** *Firmicutes.*
- **Class:** *Bacilli.*
- **Order:** *Bacillales*
- **Family:** *Staphylococaceae.*
- **Genre:** *Staphylococcus.*
- **Species:** *Staphylococcus aureus.*

The species of the genus *Staphylococcus* are classified into two groups according to their capacity to produce or not a free active coagulase on rabbit plasma. Noting that Coagulase-positive Staph are the most virulent strains.

Coagulase positive *Staphylococcus*: *S. aureus*

Coagulase negative *Staphylococcus*: *S. epidermidis, S. saprophyticus* (Ghanem, 2017).

1.2.3 Habitat:

Staphylococci are ubiquitous germs, very widespread in nature, found in soil, dust, water and certain food products like milk, dairy products and meat. Surviving for several months in the environment if they are protected from drought and desiccation. They also are very frequent commensals of the skin and natural cavities of mammals and birds with a predominance in the nostrils, nasopharynx, perineum, intestinal and genital tract (May, 2006).

1.2.4 Transmission:

Staphylococci can be transmitted by direct contact, or by indirect contact through air, water, food, during suckling (in case of mastitis) or by living vectors, inanimate objects or contaminated surfaces (Denis *et al*., 2016).

It is a zoonosis, transmitted from human to human, animal to human and vice versa. A study in the Netherlands, based on the comparison of strains of human origins (44 strains of S. aureus isolated from the nostrils of pig farmers) and others of animal origins (14 infected pig strains) showed that four MRSA ST389 strains of porcine origin are identical to the six strains of human origin. In short, it was concluded that there was a high risk of over-colonization of farmers and slaughterhouse by S. aureus with a risk of ST389 suggesting perpetual exchanges of strains between animals and humans (Armand-Lefevre *et al*., 2005).

1.2.5 Source and reservoirs in the farms:

Several sources of bacteria can be considered in livestock. The main being represented by the animals themselves and the secondary sources are represented by: the breeding ground, the litter, the food, the air, the insects, the equipment but also the other animals present in the farm. The hands and the nasal flora of the workers, breeders and veterinarians are also a considerable source (Budd *et al.*, 2015).

1.2.6 Resistance in the environment:

S. aureus is naturally, chemically and physically robust and can tolerate ranges of pH of 4.5-9 and a concentration of the NaCl up to 9%. *S. aureus* suspended in 0.9% of NaCl is quickly inactivated at 46°C. When protected by protein (such as milk or pus), *S. aureus* is able to survive up to 50 minutes at 60°C. It can also acquire genes that give it a resistance to specific classes (Andreoletti et al., 2009). These bacteria survive on carcasses and organs (up to 42 days), floors (less than 7 days), glass (46 hours), in the sun exposed environment (17 hours), at UV (7 hours), in meat products (60 days), on the skin (30 min to 38 days) (Neely and Maley, 2000).

1.2.7 Virulence factors:

S. aureus have the ability to infect a human or animal in a multitude of ways. The severity of the infections caused by S. aureus is associated with its virulence factors which allow it to adhere to surface, invade or avoid the immune system, and cause harmful toxic effects to the host. The majority of these factors are regulated by numerous systems, the most general being: Accessory Gene Regulator *(Agr)* (Robert, 2013).

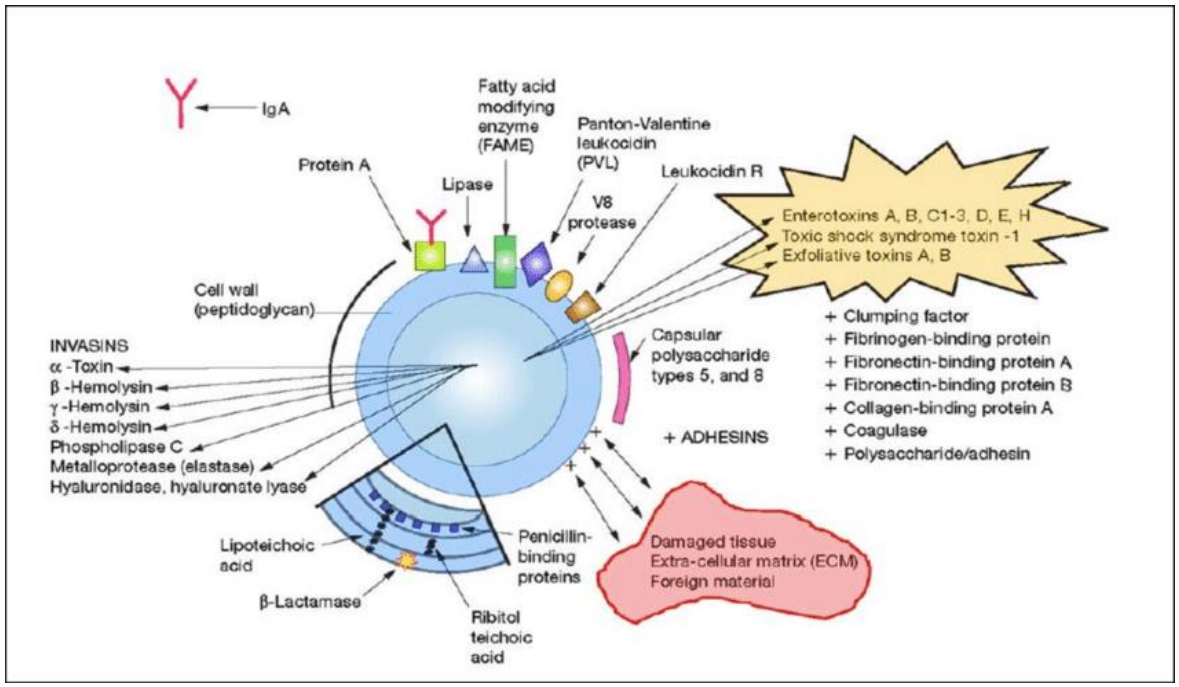

Figure 1: Scheme of virulence factors in S. aureus (Natheer, 2019)

1.2.7.1 Antigens:

They are surface proteins that allow the bacteria to attach to the extracellular matrix, and are especially useful at the onset of infection to allow tissue colonization (Le Minor and Véron, 1990).

Table 1: Biological properties of *S. aureus* Antigens (Le Minor and Véron, 1990)

Antigenic element	Nature of the element	Biological properties
Peptidoglycan	Polysaccharide polymer	-Activity on B lymphocytes. -Induce immunosuppressive cells. -Endotoxin and pyogenic effect. -Complement activation.
Protein A	Holoprotein	-Fix the Fc fraction (constant fragment) of human IgGI immunoglobulins. -Inhibits opsonophagocytosis. -Binds to Von Willebrand factors causing infectious endocarditis. -Activation of complement.
Teichoic acids	Linear glycerol polymer	-Role in the binding and transport of cations (Mg ++). -Interactions between bacteria and cells. -Binding of bacteriophages
Surface antigens	Polysaccharides	-The capsule surrounding the bacteria and allows it to adhere to exterior surfaces. -Has an antiphagocytic effect, render the bacterium resistant and contribute to its persistence in the bloodstream of infected hosts. -Promotes abscess.

1.2.7.2 Toxins:

S. aureus has the ability to produce a number of toxins, grouped according to their mechanisms of action as follows:

- **Hemolysin:** hemolysin A or alpha or Staphylolysin A is cytotoxic and cytolytic, with pro-inflammatory and antigenic properties, causing staphylococcal septic shock, and a necrotic effect on the skin. It is synthesized by 80-90% of the strains.

Table 2: Mains toxins produced by *S. aureus* (Nair *et al*., 2000)

Hemolysin:	Nature:	Biological effect on host:
Hemolysin α:	antigenic thermostable protein	-Cytotoxic and cytolytic for a wide variety of cell types. -Results in the production of antitoxins which prevent binding to the membrane.
Hemolysin β:	type C phospholipids	-Active on sphingomyelin, hence the name sphingomyelinase type C. -Hemolytic activity.
Hemolysin γ:	Two factors I and II acting in synergy	-Hemolysis. -Lysosomal rupture
Hemolysin δ:	Thermostable and hydrophobic protein	detergent on plasma membranes, active on erythrocytes, macrophages and granulocytes.

- **Staphylococcal enterotoxins:** produced by certain strains of *S. aureus*, responsible for clinical digestive manifestations (food poisoning). These are thermostable proteins, insensitive to the proteolytic enzymes of the digestive juice, with an action on lymphocytes T.
- **Exfoliatin or Epiderolysin:** there are two proteins, A and B. Exfoliatin A is thermostable and of chromosomal origin, while exfoliatin B is thermolabile of plasmid origin. Responsible for cutaneous staphylococci, causes intra epidermal cleavage, and provokes Staphylococcal Scalded Skin Syndrome (SSSS) in children, and impetigo (Le Minor and Véron, 1990).
- **Panton-Valentine leukocidin:** composed of two subunits S and F, acting in synergy on granulocytes, basophils and macrophages causes them loss of mobility, degranulation, nuclear destruction and cell lysis. It has an important role in the formation of pus. With leucotoxic due to a change in cationic permeability, and dermonecrotic properties causing primary skin infections, especially boils but also necrotizing pneumonia (Otto, 2014).
- **Staphylococcal toxic shock syndrome toxin TSST-1:** sensitive to proteolytic enzymes, capable of super antigenic activity and causes toxic staphylococcal shock.

1.2.7.3 Enzymes:

Staphylococci produce enzymes responsible for the destruction of tissues, and the spread of bacteria within tissues. They are highlighted in **Table 3.**

Table 3: Main enzymes produced by *S. aureus* (Bouchakour, 2014)

Enzymes	Biological activity
Free Coagulase:	-Produces in a few hours a substance capable of coagulating human or rabbit plasma. -This substance is thermostable, secreted during the exponential phase of germ growth. -It has a role in the formation of suppurative thrombophlebitis and inhibits phagocytosis
Fibrinolysin or Staphylokinase:	-Thermolabile and antigenic plasminogen activator substance, acting on human or rabbit plasma.
Hyaluronidase:	-Thermolabile enzyme. -Hydrolyzes hyaluronic acid and promotes the diffusion of staphylococci into connective tissues
Nuclease:	-Thermostable enzyme. -Hydrolyzes DNA and RNA

1.3 Bacteriological diagnosis of S. aureus:

1.3.1 Morphological characters:

Staphylococci are Gram (+) cocci (round), nonmotile and does not form spores immobile, it possesses no capsule, except for very rare strains that have a pseudo-capsule. Isolated or grouped in diplococci, tetrads, in short chains or most often in clusters of several elements. Its diameter is on average 0.8-1µm. They are facultative aerobic, heat resistant, with low DNA (G + C) content (in the range of 30-40%), and tolerance to high salt concentration.

Gram (+) bacteria, does not carry an outer membrane, the peptidoglycan layer is much thicker (from 20nm to 80nm) where molecules of teichoic acids are inserted (Denis *et al.*, 2016).

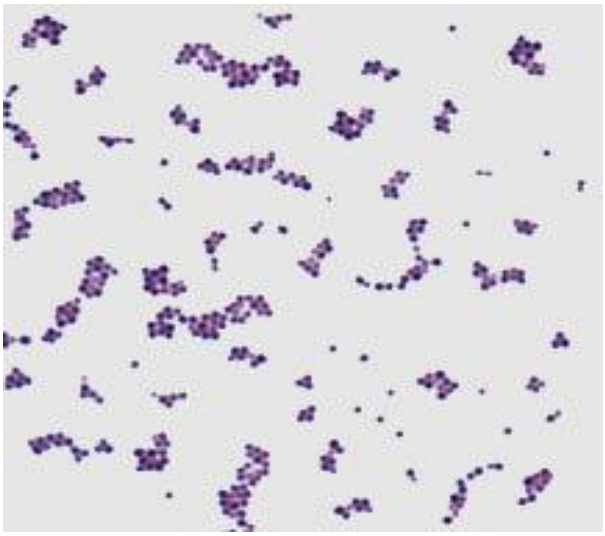

Figure 2: *Staphylococcus aureus* in cluster chains and singles arrangements isolated from sheep nasal swab (10µm) (Mamza *et al.*, 2016)

1.3.2 Cultural characters:

They are undemanding germs, and can be isolated in broth or on solid media, such as ordinary agar or blood agar at 35-37 ° C under aerobic conditions. On usual media, the colonies are round, golden-yellow of variable sizes (1 to 3 mm), circulating, smooth, opaque, slightly convex or flattened. *Staphylococcus aureus*, the most invasive species is coagulase-positive, and often produces a carotenoid yellow pigment, hence the name "golden staph" (Couture, 1990).

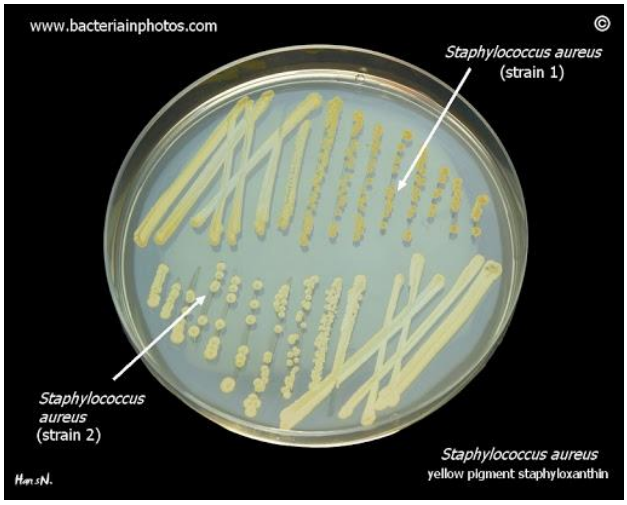

Figure 3: Two strains of *Staphylococcus aureus* on Tryptic Soy Agar, different shades of yellow pigmentation (Bacteria in Photos, 2011)

1.3.3 Biochemical characters:

The main biochemical characters of *Staphylococcus aureus* are resumed in **Table 4.**

Table 4: Biochemical characteristics of *S. aureus* (Guiraud and Rosec, 2004)

Coagulase (free or bound)	**+**
Mannitol acidification	**+**
Nitrate reductase	**+**
Protein A	**+**
Sensitivity to Novobiocin	**+**
Glucose	**+**
Lactose	**+**
Indole	**-**
Oxidase	**-**
Catalase	**+**
Thermonuclease (DNAse)	**+**

1.4 Pathogenicity:

The genus Staphylococcus contains species which are part of the normal flora of humans and animals, acting as a commensally bacterium, lying dormant in the body for years undetected, asymptomatically colonizing about 30% of the human population. But under certain conditions can become major opportunists. *S. aureus* as the most pathogenic species, is the source of numerous and different infections, the prevalence of which constitutes a major public health problem, due to their virulence, their resistance to antibiotics and epidemic power (Bouchakour, 2014).

1.4.1 In humans:

Suppurative infections are the most frequent, they are abscesses, boils, phlegmons, pleurisy, peritonitis, arthritis, osteomyelitis. Septicemic staphylococci occur most often in a hospital environment due to contamination. Noting that nosocomial infections can result from auto-infection by patient strains, or from cross-transmission (patient / staff, infected or colonized), generally following a cutaneous-mucous infection which often goes unnoticed, accompanied by various visceral localization: pleuropulmonary, osteo-articular, neurological, genitourinary and cardiovascular (Wertheim *et al*., 2005).

Food poisoning though, is caused by the ingestion of the thermostable enterotoxin produced by strains of S. aureus and contaminating the food. The most often incriminated are dairy products and meat (Wertheim *et al*., 2005).

1.4.2 In Animals:

Skin diseases constitute the bulk of staphylococcal infections reported in animals. Suppurative dermatitis (pyoderma), superficial or deep, is reported in livestock and in many other animal species. Skin abscess and cellulitis are common in horses, *S. aureus* may also be associated with otorhinolaryngological infections (otitis, upper respiratory tract super-infections in the dog and cat), urinary tract infections in many species, metritis (cow, dog), cystitis (all species), abscesses (perirenal, lung), osteomyelitis or endocarditis, pleurisy, peritonitis, or arthritis, especially in poultry. It is also a cause for Botriomycosis, a pyogranulomatous inflammation of the udder of mares, cows and sows (mastitis) and of the spermatic cord in horses following castration. It has also been reported in wild animals (Peton and Le Loir, 2014).

- **In Ruminants (cattle / sheep / goats):**

Staphylococcus aureus is a major bovine mastitis pathogen responsible for heavy economic losses in dairy industry, also causing contagious metritis and mastitis in sheep, and goats. This mastitis takes on different aspects such as gangrenous mastitis, the most dreadful form which can go as far as tissue necrosis and causes milk retention, acute and most often chronic mastitis (Akkou *et al.*, 2016).

Cutaneous Staphylococci are sporadic or enzootic infections of the skin, due to inoculation and multiplication S aureus. Causes suppurative infections, pustular dermatitis, furunculosis, folliculitis with abscess formation. The most frequent lesions are found mainly at the base of the tail, on the croup, or in the perianal region on the one hand, on the udder and teat on the other hand (Monecke *et al.*, 2007).

- **In Canines:**

Infectious otitis externa is usually a secondary complication due to the presence of *S. pseudintermedius* in ears, S. aureus is rarely isolated, in dogs, *S. aureus* is rarely involved found, except some cases of suppurative dermatitis and mastitis in dogs (Peton and Le Loir, 2014).

Table 5: Most common infections caused by *Staphylococcus aureus* in animals (Peton and Le Loir, 2014)

Host	Infections
Bovine	Mastitis, impetigo
Sheep	Mastitis, dermatitis, mild folliculitis
	Lymphadenitis, abscess disease
Goat	Mammary Botryomycosis
Pig	Mastitis, castration wounds
Horse	Dermatitis, urinary tract infections and abscesses
Cat / Dog	Dermatitis, abscesses, Cystitis and suppuration.
Poultry	Arthritis, septicaemia, Bumblefoot (pododermatitis)

2 Staphylococcus aureus and Antibiotic resistance:

In October 2015, the World Health Organization (WHO) launched the Global Antimicrobial Resistance Surveillance System (GLASS), which currently includes eight organisms, one of which is *Staphylococcus aureus* (WHO, 2015). Key drug classes for antimicrobial susceptibility testing (AST) include Penicillin, Cephalosporins (3GC and 4GC), Carbapenems, Fluoroquinolones, Aminoglycosides, Tetracyclines, Polymyxins, Macrolides, and Co-Trimoxazole.

2.1 Resistance to β-lactam antibiotics (Penicillin & Methicillin):

It appeared soon after the introduction of the antibiotic, and is due to the production of penicillinase, an extracellular enzyme that hydrolyses penicillin. Today, more than 90% of S. aureus isolates are penicillin resistant (de Lencastre *et al*., 2007). Methicillin, the prototype of the anti-staphylococcal penicillin, was designed to resist the action of penicillinase, but *S. aureus* developed a resistance mechanism to it. The resistance mechanism involves acquisition of the *mecA* gene, the determinant penicillin binding protein termed PBP2a, that has reduced affinity for methicillin, and can can continue peptidoglycan synthesis in the presence of the antibiotic. Before 'arriving' to *S. aureus* the *mecA* gene has to be incorporated into a unique molecular vector called the staphylococcal chromosome cassette (SCC), which is capable of delivering a variety of different resistance or virulence determinants to S. aureus, including *mecA* (de Lencastre et al., 2007; Deurenberg *et al*., 2007).

For the first three decades after their appearance, MRSA strains typically have remained hospital associated pathogens (HA-MRSA). Then, unexpectedly, MRSA strains causing serious infection in the community, termed community acquired (CA)-MRSA, have emerged, appearing amongst people with none of the usual risk factors for such infections. They are generally susceptible to most non-β-lactam antibiotics, contains *SCCmec* type IV and a toxin, the Panton-Valentine leucocidin (Pantosti et al., 2007).

2.2 Resistance to Glycopeptides (Vancomycin):

Vancomycin represents the cornerstone of therapy for MRSA. However, at the end of the last decade, strains appeared that are intermediately resistant (VISA) or fully resistant (VRSA) to vancomycin (Appelbaum, 2006).

2.2.1 Vancomycin Intermediate *Staphylococcus aureus* VISA :

Resistance in VISA strains occur as a result of changes in peptidoglycan synthesis, with increased quantities of *D-Ala-D-Ala* residues that bind vancomycin molecules and effectively preventing them from reaching the true targets in the glycopeptide's precursors at the inner layer of the cell wall. The genetic basis of this mechanisms is unknown (Appelbaum, 2006).

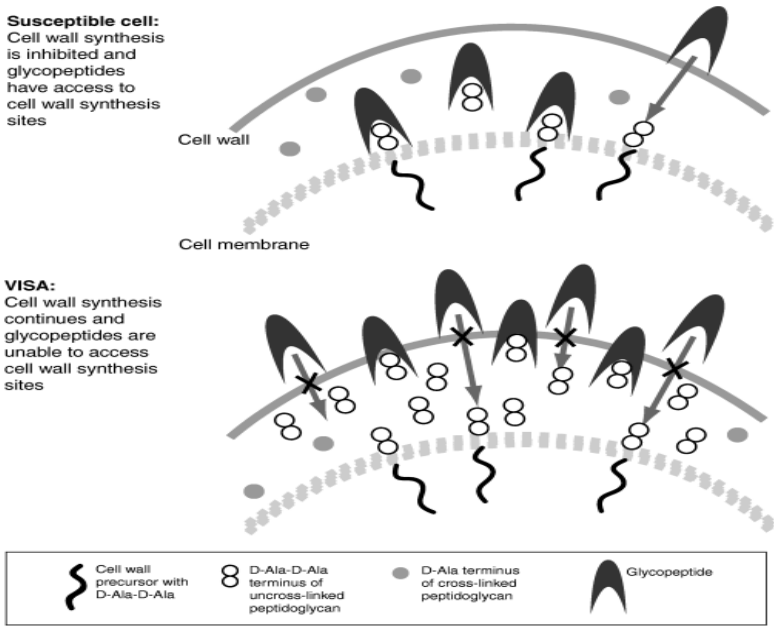

Figure 4: Mechanism of vancomycin-intermediate *Staphylococcus aureus* (Appelbaum, 2006)

2.2.2 Vancomycin Resistant *Staphylococcus aureus* VRSA :

Glycopeptides exert their antimicrobial effects by inhibiting synthesis of the S. aureus cell wall. The mechanism of resistance in (VRSA) is identical to that of vancomycin-resistant enterococci, the vancomycin target *D-Ala-D-Ala* is replaced by *D-Ala-D-Lac*, and this modification causes a dramatic reduction of affinity for the antibiotic. To date, six VRSA strains have been acquired

from VRE, by HGT of a transposon carrying the vancomycin resistance operon *vanA,* likely with a plasmid acting as a vector (Appelbaum, 2006).

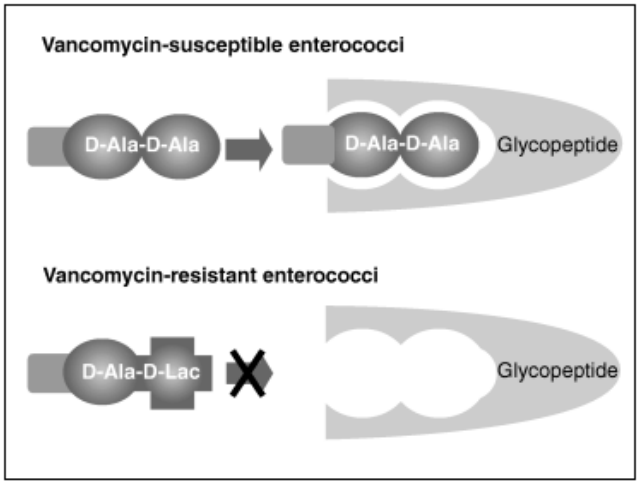

Figure 5: Mechanism of vancomycin-resistant *Staphylococcus aureus* (Appelbaum, 2006)

2.3 Resistance to Linezolid & Daptomycin:

Two new antibiotics, very active against MRSA strains, Linezolid and Daptomycin. Few linezolid-resistant isolates have been isolated, with single-nucleotide mutation in the ribosomal binding site for linezolid. Strains with reduced daptomycin susceptibility arising during therapy have been identified. Resistance is associated with multiple mutations and involves modification of the bacterial membrane potential. Daptomycin is less active against VISA, suggesting that antibiotic trapping could play a role (Pantosti *et al*., 2007).

3 Epidemiological situation of *Staphylococcus aureus* in Algeria:

Overall prevalence of *S. aureus* in Algeria:

A study by (Mairi *et al.*, 2019) aiming to estimate the prevalence of *S. aureus* strains recovered in a large collection of samples obtained from 12 Algerian provinces. 2246 samples were collected in total, and only 312 *S. aureus* isolates obtained from 312 samples were identified giving an overall prevalence of 12.7%.

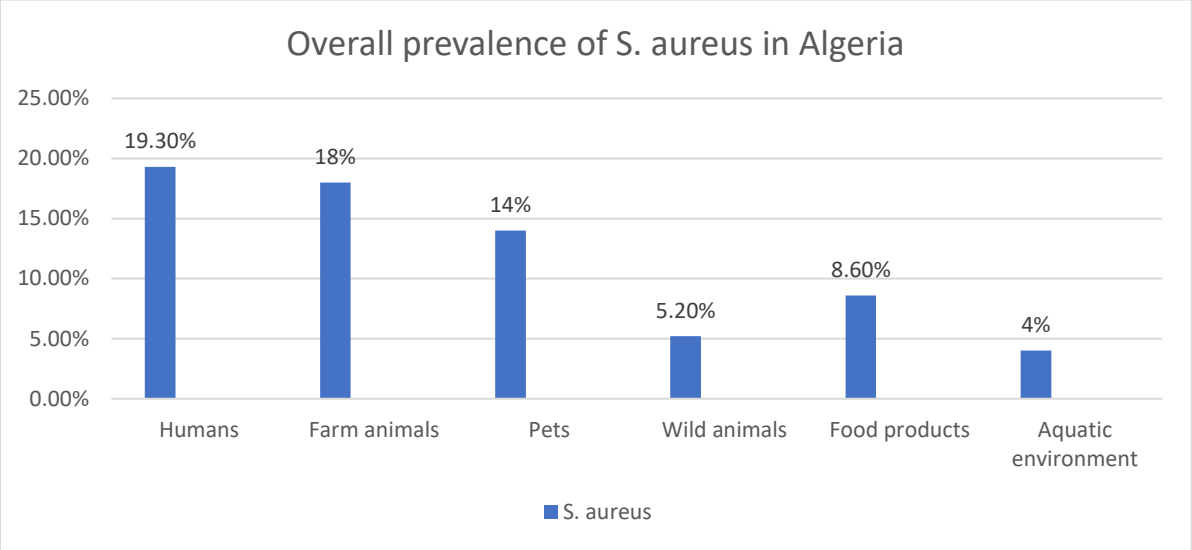

Figure 6: Overall prevalence of S. aureus in Algeria (Mairi *et al.*, 2019)

The study obtained a global MRSA prevalence of 6.4%.

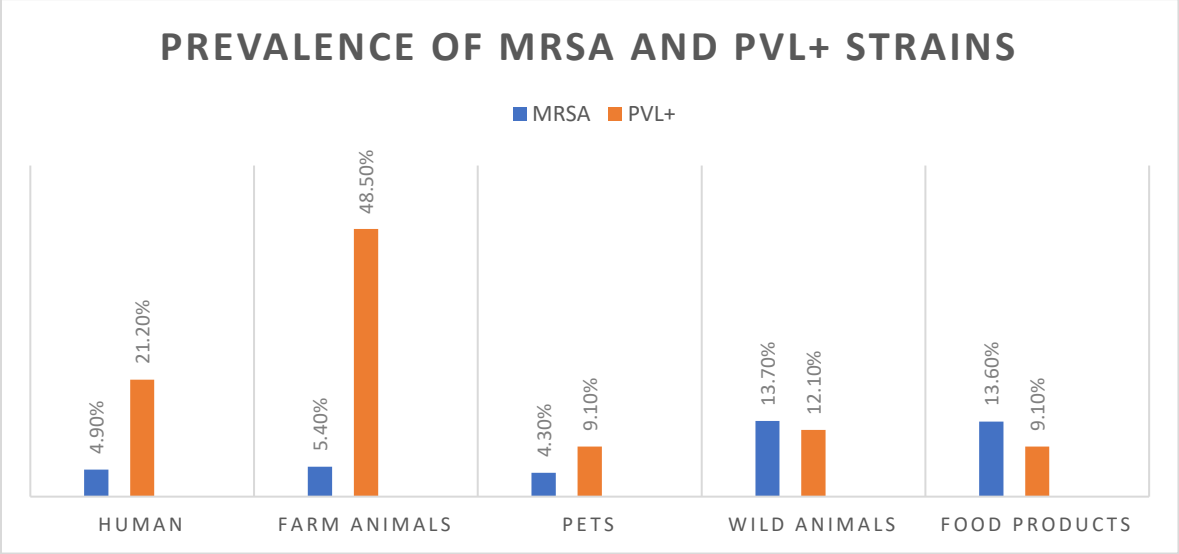

Figure 7: Prevalence of MRSA and PVL+ strains (Mairi *et al.*, 2019)

3.1 Diffusion of *Staphylococcus aureus* in human health:

3.1.1 In the hospital environment:

A study of (Basset *et al.*, 2015), recovered MRSA isolates (n = 84) between the period of January 2006 to July 2011 from the Bologhine Ibn Ziri University hospital (250 beds) in Algiers (Algeria). The study tested the susceptibility to 12 common antimicrobial agents using the disc-diffusion method according to the Clinical and Laboratory Standards Institute (CLSI) guidelines.

The following table shows the results of resistance and susceptibility of all MRSA isolates to antibiotics.

Table 6: Patterns of susceptibility of the European CA-MRSA and Brazilian clones as well as overall Algerian MRSA isolates (Basset *et al*., 2015)

	Resistant isolates (%) among:		
Antibiotic	**European CA-MRSA isolates ST80 (n=72)**	**(Brazilian MRSA isolates ST239 (n=7)**	**All isolates (n=84)**
Penicillin	100	100	100
Oxacillin	100	100	100
Cefoxitin	100	100	100
Kanamycine	69.3	100	77.4
Tetracycline	55.6	71.4	58.3
Clindamycin	8.3	0	9.5
Co-trimoxazole	20.8	57.1	23.8
Ofloxacine	8.3	71.4	15.5
Rifampin	0	0	0
Vancomycin	0	0	0
Teichoplanine	0	0	0
Fusidic acid	55.6	42.9	53.6

Among the 84 MRSA isolates, 13 different DLST types were described, related to international clones. The analysis identified two main clusters as well as three singletons, the first main one with DLST ancestor 415-26 represents 85.7% (72/84) of all isolates, corresponding to the European CA-MRSA clone (ST80), all isolates of this clone were PVL positive, and carry the SCC *mec* type IV.

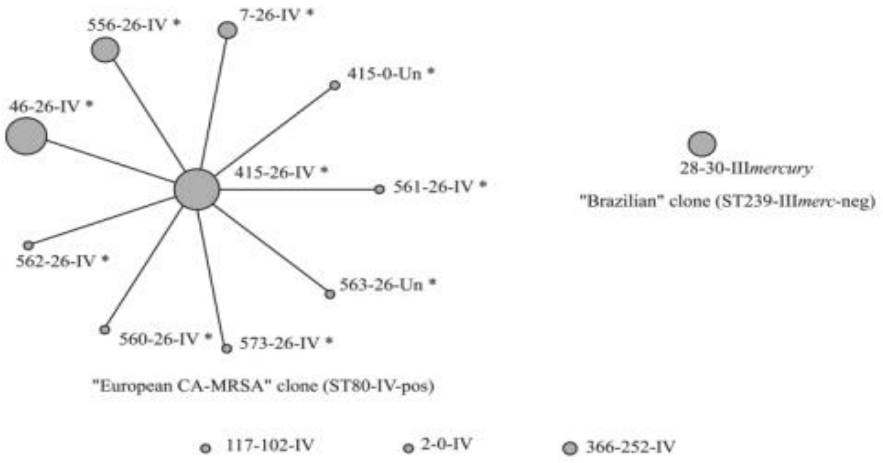

Figure 8: DLST single-locus variant clustering of 84 S. aureus isolates from the Bologhine Ibn Ziri University hospital in Algeria using eBURST. (Basset *et al.*, 2015)

(Each circle represents one DLST type, and the diameter of the circle reflects the frequency (i.e., the number of isolates) of that type. Linked DLST types differ at one of the two loci (clfB or spa). SCCmec type is indicated next to each DLST type ("Un" indicates isolates with unknown ccr type) and each DLST types including PVL-positive isolates are indicated by asterisks. Two isolates had a null allele (i.e. 0) at the spa locus. The name of the international clone associated with each of the main cluster is indicated under the cluster.)

The second cluster, with DLST type 28-30 represents 8.3% (7/84) of all isolates, related to the Brazilian clone (ST239), all isolates of this clone carried the SCC*mec* III*mercury* and were PVL negative.

The European CA-MRSA (ST80-IV-pos) is the most common community acquired clone in Europe, but is also from North African countries. And even though this clone is community-acquired, its widespread occurrence in Algerian hospitals indicates it has invaded the hospital setting.

Remarking that the proportion of isolates belonging to ST80 changed during the study period, Whereas the proportion of the Brazilian and European CA-MRSA clone observed in 2006 were close (36% vs. 43%), the European CA-MRSA clone accounted for > 90% of the isolates in the following years.

Table 7: Number of isolates belonging to the European CA-MRSA and Brazilian clone per year (Basset *et al*., 2015)

Year	European CA-MRSA clone	Brazilian clone	Other	Overall
2006	6	5	3	14
2007	9	0	0	9
2008	19	0	1	20
2009	26	0	0	26
2010	6	2	0	8
2011	6	0	1	7
Overall	72	7	5	84

In conclusion, the data confirmed the predominance of the PVL-positive European CA-MRSA (ST80-IV-pos) clone in Algeria.

Nasal carriage of S. aureus:

Another study was carried by (Djoudi *et al*., 2015), during a period of 27 months in two health care facilities in the region of Bejaya, Algeria; Frantz-Fanon Nephrology department (32 beds), Amizour (240-bed), with the objective of evaluating nasal carriage and rating of *Staphylococcus aureus* in health-care settings.

Samples were taken with sterile nasal swabs introduced in each nostril to a depth of 1cm and rotated five times. The presence of the *mec*A gene of MRSA strains was confirmed by PCR, and the susceptibility of the MRSA isolates was tested against 12 antimicrobial agents using the disk diffusion method.

Multiplex PCR was performed to identify the staphylococcal cassette chromosome *mec* element (SCC*mec*) types I to VI. To define the sequence types (ST) of MRSA strains, multilocus sequence typing (MLST) was performed and strains were assigned to STs using the MLST database. *Spa* typing was also carried out on the MRSA-ST22-IVa isolates using the Ridom StaphType software.

One hundred fifty-nine (26%) out of the 612 patients enrolled were carriers of *S. aureus*. Nine (1.5%) out of them carried MRSA, the remaining 150 (24.5%) carried methicillin susceptible *S. aureus* (MSSA).

Results are highlighted in **(Table 8)**

Table 8: Epidemiological and molecular Characteristics, and Resistance Patterns of MRSA strains in Algeria (Djoudi *et al.*, 2015)

Strain code	SCC*mec* type	Pvl/tst1 genes	ST	Resistance pattern
25	IVc	-/-	5	TOB, GEN
148	IVa	-/-	80	TOB, GRN
165	IVa	-/+	22	TOB, SXT
193	IVc	+/-	80	TE
414	IVa	-/+	22	TOB, SXT
248	IVc	+/-	80	**ERY**
257	IVc	+/-	80	TOB, GEN
296	**VII**	-/-	5	TE
322	**IVh**	-/-	**535**	TOB, TE

(ERY: Erythromycin, Gen: gentamycin, SXT: trimethoprim/sulfamethoxazole, TE: tetracycline, TOB: tobramycin.)

This study detected a higher rate among patients admitted to the nephrology department, and generally submitted to hemodialysis, which is a major risk factor (application of invasive devices such as catheters and fistulas). *S. aureus* carriage also proved to be associated with previous hospitalization, a recurrent event in the clinical course of subjects affected by kidney failure.

Four MRSA isolates were ST80, all carrying SCCmec IV, PVL genes positive, which was expected considering the dominant role of this clone in staphylococcal infections in Algeria.

There was a heterogeneity in the MRSA strains isolated, compared to the large predominance of ST80-IV in the previous investigations. The two tst1 positive ST22-MRSA-IV strains, spa type t223, were similar to the “Gaza strain”, which is predominant in healthy children and their parents in the Gaza strip. The detection of this CC22-MRSA-IV “Middle Eastern Variant” clone in Algeria confirms its wide dissemination in the Mediterranean and Middle East area.

3.1.2 In the population in contact with animals:

3.1.2.1 Farm workers:

A study by (Agabou *et al.*, 2017), carried out in the period of September 2015 to February 2016, on camels, horses, cattle, sheep and monkeys, as well as 20 consenting healthy persons (humans) in contact with these animals: cattle farmers, camel keepers, horse owners, horse riders, horse workers and veterinarians, by collecting nasal samples, from farms in three Algerian provinces (Tamanrasset, Ouargla and Constantine), and DNA microarray was used to

genotype S. aureus isolates, revealed that cattle farmers (n = 5), more colonized than horse owners/riders at (n = 4), camel keepers (n = 1) and veterinarians (n = 1).

A subset of 66 non-repetitive isolates was selected for molecular analyses. The Alere StaphyType DNA microarray was used. DNA microarray analysis was carried out for a subset of 66 *S. aureus* isolates to determine their genetic diversity (12 from humans, 23 from camels, 19 from sheep, six from cattle, five from horses and one from a monkey)

Table 9: Clonal complex distribution of the Staphylococcus aureus strains isolated from nasal samples of livestock (A) and humans (H) in contact with them in three Algerian provinces (Agabou *et al*., 2017)

Clonal Complex	Clone assignment	Humans	Horses	Camels	Cattle	Sheep	Monkeys
CC130	ST130 ST130-MSSA			+		+	
CC1	ST1-MSSA ST1278-MSSA	 +	+	 +	+		
CC8	ST8-MSSA ST72-MSSA	+	+			+	 +
CC6	ST6-MSSA					+	
CC80	ST80-MRSA IV					+	
CC88	ST88-MSSA			+			
CC97	ST97-MSSA					+	
CC15	ST15-MSSA	+			+		
CC133	ST133-MSSA					+	
CC705	ST705				+		
CC152	ST152-MSSA			+			
CC30	ST30-MSSA			+			
CC45	ST45-MSSA		+				
CC398	ST398-MSSA	+					
CC22	ST22-MSSA	+					

CC130 included camels and sheep isolates, CC1 grouped human, horse, camel and cattle isolates, CC8 contained human, horse, sheep and monkey isolates and CC15 gathered human and cattle isolates. CC6 and CC80 were exclusive to sheep, CC88, CC152, CC30 were limited to camels, CC398 and CC22 were specific to humans, and CC45 to horses whilst CC88 was specific to cattle.

Isolates belonging to the ST80-MRSA clone were identified in healthy sheep and camels, from Constantine (northeast of Algeria) and Tamanrasset (south), located 2050 km apart, suggesting that this clone has already spread across the country and North Africa. The ST152 PVL+ clone is

frequent in West Africa (40–60% of the *S. aureus* strains), but was never before described in Algeria. ST152 PVL+ MSSA was identified in a camel from a southern province on borders with Mali, meaning this clone is already established in camels and humans in the region.

Epidemic PVL+ clones are noted in red. Clones with potential animal origin are noted in green. The other clones are noted in blue

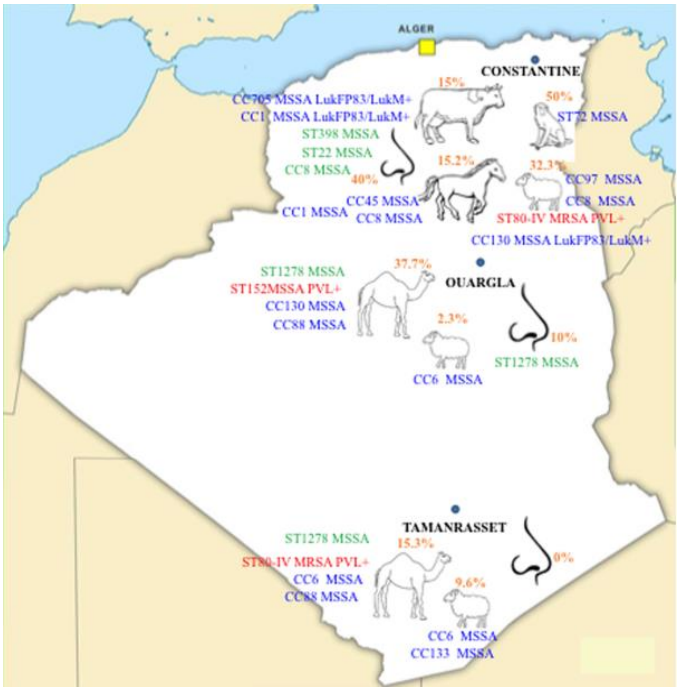

Figure 9: Main *S. aureus* clones circulating in Algeria among animals and humans in contact with them. (Agabou *et al.*, 2017)

The presence of MSSA-ST1278, a rarely and poorly characterized singleton of CC1, in isolates from camels in Ouargla and Tamanrasset provinces, as well as a camel keeper in Ouargla province.

The presence of a variety of CCs in animals and humans, and the discovery of classical human CCs (e.g., CC1, CC8, CC15, CC30, C45) in animals suggests a possible transmission from humans. However, the detection of CCs specific to animals in humans (CC97, CC130, CC133, ST398 and ST705) indicates an acquisition through occupational contact. The transmission seems to be more complex with the presence of several reservoirs (environment, other animal species or animals from the same species) (Budd *et al*., 2015). For example, ST398 was found in a horse worker and a veterinarian in the Constantine region, which could suggest the possession of this livestock-associated lineage by further animals (e.g., horses and poultry) not screened in the study.

In animals, the prevalence of *S. aureus* nasal carriage varies between the species: horses (7.9%), cattle (46.5%), camels (53%), and monkeys (58%).

Some *S. aureus* genes are specific to humans (*sak, chp, scn, hlb, sea*), their absence is a valuable indicator of *S. aureus* livestock adaptation (Sung *et al.*, 2008), which was confirmed with the absence of these markers in animal isolates. ST80 Isolates were tested positive to *sak* and *scn* genes, confirming their human origin, except for one ST80 isolate from a sheep that was negative to all these genes, suggesting an adaptation to its animal host.

Some ST97, ST151, CC705 isolated from cattle and humans acquired foreign DNA absent from *S. aureus* of human origin.

For instance, horizontal transfer of a chromosomal cassette confers the ability to produce toxins such as PVL. Toxins, such as PVL is a factor in serious infections in humans. However, PVL-positive strains are rare in animals. This study identified lukF/S-PV genes in six ST80-MRSA strains from six sheep and two camels, and a ST152-MSSA isolate from a camel.

This study showed the dispersal of some highly pathogenic clones ST152-MSSA-PVL+ and ST-80-MRSA-PVL+, and suggested the ability of some clones to cross the species barrier and jump between humans and several animal species. These findings support the hypothesis that animals are potent reservoirs of multidrug-resistant and toxinogenic bacteria.

3.2 *Staphylococcus aureus* in food of animal origin:

3.2.1 Characterization of *Staphylococcus aureus* Isolated from Food Products:

Food and food production may be a vehicle of antibiotic resistant bacteria and antibiotic resistance dissemination, which can be transmitted through the consumption of food animal products, including unpasteurized milk, meat or fish products (Authority, 2008), it is considered an important vehicle for the spread of antibiotic-resistant bacteria , and Staphylococci are the most isolated bacteria in foodborne illnesses globally, also involved in severe systemic affections.

According to a study by (Chaalal *et al*., 2018), on different samples of foodstuffs collected from poultry slaughterhouses, butcheries, farms, and supermarkets, and University cities mainly from the western Algeria, between November 2014 and November 2015 for contamination with *S. aureus*.

Table 10: Prevalence of *S. aureus* and MRSA in Foodstuffs in Western Algeria (Chaalal *et al.*, 2018)

Food products	**Number of samples:**	**Contaminated samples:**	**MRSA**		
			mecA	***pvl***	***tsst***
Total:	495	153	26 (16.9%)	17 (11.1%)	5 (3.2%)
Fresh (raw) meat ➢ **Poultry** ➢ **Lambs** ➢ **Calves**	109 ➢ 35 ➢ 40 ➢ 34	45 (29.4%)	9 (20%)	4 (8.8%)	/
Raw milk	141	50 (32.6%)	11 (22%)	9 (18%)	2 (4%)
Pasteurized milk	60	14 (9.1%)	2 (14.2%)	/	1 (7.1%)
Pastry	80	23 (15%)	1 (4.3%)	2 (8.7%)	1 (4.3%)
Cooked samples: ➢ **Chicken** ➢ **Beef**	105 ➢ 60 ➢ 45	21 (13.7%)	3 (14.3%)	2 (9.5%)	1 4.7%)

- **Prevalence of *S. aureus* and MRSA in food:**

S. aureus was detected in 30.9% (153/495) of the collected food items **(Table 10)**. 40 *S. aureus* isolates exhibited methicillin-resistance phenotype. A high prevalence of PVL-encoding genes was found in MRSA isolates, this toxin is typically associated with certain CA-MRSA strains but generally lacking in LA-MRSA. The *mecC* gene was not detected in any isolate. The remaining 120 isolates were MSSA (78.4% of *S. aureus*) carriers.

This study (Chaalal *et al*., 2018) conducted that 30.9% were contaminated by *S. aureus*, out of which 32.6% and 29.4% were recovered from raw milk and raw meat, respectively. These results do not differ much from previous results by different studies in Africa.

These finding are to be expected, as protein-rich foods harbor *S. aureus* and are associated with food poisoning. The food contamination with *S. aureus* is often due to infected food handlers during the processing stage. The vulnerability of *S. aureus* heating and sanitizing agents; means that its presence in processed foods is generally indicative of poor hygiene.

33.3% (51/153) of *S. aureus* isolates displayed resistance to three or more antimicrobial drugs, imposing thus a severe public health threat in Algeria.

All this is to say that food is an excellent way for introducing *pvl*-positive MRSA isolates and also for *S. aureus* isolates carrying the *tsst* gene in general population. The risk of transmission of *S. aureus* and MRSA carrying different antimicrobial resistance and virulence genes through the food chain cannot be ignored, especially in raw milk and fresh meat. The antimicrobial resistance patterns of this organism may be suggestive of the extent of misuse of antibiotics in medical and veterinary practices in Algeria (Chaalal *et al.*, 2018)

3.2.2 Phenotypic antimicrobial resistance associated genes of *S. aureus* in Food:

In order to determine phenotypic antimicrobial resistance and associated genes of staphylococci isolates from food samples in Algeria, a study by (Achek *et al*., 2018) was carried out. One hundred and twelve food samples, raw milk (n=30), minced beef meat (n=25), chicken meat (n=18), creamy cake (n=14), pizza (n=10), beef meat (n=10) and sausages (n=5) were collected from retail markets in two provinces in Algeria (Medea and Ain Defla).

Antimicrobial susceptibility to 12 antimicrobial agents was tested using the disc diffusion test, genomic DNA was extracted and PCR was used to detect resistance-associated genes.

51 Staphylococci, isolated from food samples were identified (33 *S. aureus*, and 18 CoNS (Coagulase negative Staphylococci), 49 out of 51 (33 *S. aureus* and 15 CoNS) were resistant to at least one tested antibiotic (96.1%).

Resistance rates are highlighted in **(Table 11)**, resistance rates to penicillin (94.1%), tetracycline (49.0%). One *S. aureus* was a confirmed MRSA, and another as MR-CoNS, and one *S. aureus* was

VRSA (3.0%). The resistance rates of CoNS to clindamycin (33.3%) and erythromycin (27.8%), and all isolates were susceptible to gentamicin.

The antibiotic resistance-associated genes are demonstrated in **(Table 12)**, *tetM* was the predominant gene detected in *S. aureus* (66.7%) and CoNS (88.9%). Both tetM and *tetK* genes were detected in 11 S. aureus (33.3%) and 4 CoNS (22.2%). 15 S. aureus (46.9%) and 10 CoNS (88.9%) isolates were tested positive for *mecA*. Six *S. aureus* (18.2%) and 3 CoNS (16.7%) isolates harbored gentamycin associated *aacA-aphD* gene, 15 *S. aureus* (46.9%) and 10 CoNS (88.9%) isolates possessed penicillin resistance encoding *blaZ* gene.

Table 11: Antimicrobial susceptibility of Staphylococci isolated from food samples (Achek *et al*., 2018)

Antibiotic agent	**Food isolates (n=51)**					
	***S. aureus* (n=33)**			**CoNS (n=18)**		
	S rate (%)	**R rate (%)**	**I rate (%)**	**S rate (%)**	**R rate (%)**	**I rate (%)**
P (10UI)	0.00	100.00	0.00	16.67	83.33	0.00
OX (1 µg)	93.94	6.06	0.00	83.33	16.67	0.00
FOX (30 µg)	93.94	6.06	0.00	83.33	16.67	0.00
AMC 520/10 µg)	100.00	0.00	0.00	94.44	5.53	0.00
GM (10 µg)	100.00	0.00	0.00	100.00	0.00	0.00
E (15 µg)	81.82	9.09	9.09	55.56	27.78	16.67
K (30 µg)	54.55	9.09	36.36	83.33	11.11	5.56
TE (30 µg)	54.55	45.45	0.00	44.44	55.56	0.00
VA (30 µg)	96.97	3.03	0.00	100.00	0.00	0.00
CL (2 µg)	90.91	6.06	3.03	61.11	33.33	5.56
RIF (5 µg)	96.97	3.03	0.00	88.89	11.11	0.00
STX (1.25/23.75 µg)	100.00	0.00	0.00	83.33	5.56	11.11

(P penicillin, OX oxacillin, FOX cefoxitin, AMC amoxicillin + clavulanic acid, GM gentamicin, E erythromycin, K kanamycin, TE tetracycline, VA vancomycin, CL clindamycin, RIF rifampicin, STX trimethoprim/sulfamethoxazole, S susceptible, R resistant, I intermediate)

Table 12: Distribution of antimicrobial resistance genes of food (Achek *et al*., 2018)

Antibiotic agent	**Target genes**	**Food isolates (n=51)**		***P* value**
		S. aureus (n=33)	CoNS (n=18)	
Tetracycline	*tet*M	22 (66.67%)	16 (88.89%)	0.103
	*tet*K	13 (39.39%)	4 (22.22%)	0.351
Erythromycin	*erm*A	0 (0.00%)	0 (0.00%)	ND
	*erm*C	2 (6.06%)	1 (5.56%)	1.000
Gentamicin	*aac*A-*aph*D	6 (18.18%)	3 (16.67%)	1.000
Penicillin	*bla*Z	15 (46.87%)	10 (88.89%)	0.565
Methicillin	*mec*A	15 (46.87%)	10 (88.89%)	0.565

Prevalence of *S. aureus* resistant to oxacillin in food isolates is (6.1%), all isolates were resistant to penicillin, but not all penicillin-resistant *S. aureus* isolates possessed *blaZ* gene. And whilst no resistance to gentamicin was found in staphylococci isolated in milk in previous research in Algeria, this study, stated all *S. aureus* isolates susceptible to gentamicin, with one *S. aureus* isolate exhibiting phenotypic resistance to gentamicin and possessing the *aacA-aphD* gene.

Staphylococcus aureus isolates were slightly resistant to erythromycin (9.1%), and the *ermA* gene could not be detected. The resistance of *S. aureus* isolates to tetracycline was high, and the *tetK* and *tetM* genes were detected in resistant *S. aureus*.

Vancomycin was the most effective antimicrobial agent against MRSA, and 3 *S. aureus* strains were vancomycin-resistant. Most CoNS isolates were resistant to penicillin, tetracycline and erythromycin. 16.7% of CoNS isolates were confirmed as methicillin-resistant CoNS (MR-CoNS). 75.0% of CoNS possessed the *mecA* gene, and only one (5.6%) possessed the *ermC*.

3.2.3 *Staphylococcus aureus* in raw milk traditional dairy products:

A research study carried out by (Titouche *et al*., 2019), with the aim of characterizing *S. aureus* isolates of food origin (dairy and meat products, pastries, and sandwiches) and determine the carriage in enterotoxin genes and the antimicrobial resistance pheno/genotypes.

The samples collected included raw milk (n=190) and traditional dairy products, butter (n=24), cheese (n=3), rayeb (n=24) and l'ben (n=29).

Of 270 samples of raw milk and traditional dairy products made from raw milk, 62 were contaminated with *S. aureus*. The next figure **(Figure 10)** shows the prevalence of *S. aureus* in this study. 69 S. aureus isolates were obtained from the 62 positive samples. 11 MRSA strains were identified, 9 were isolated from raw milk and 2 from L'ben.

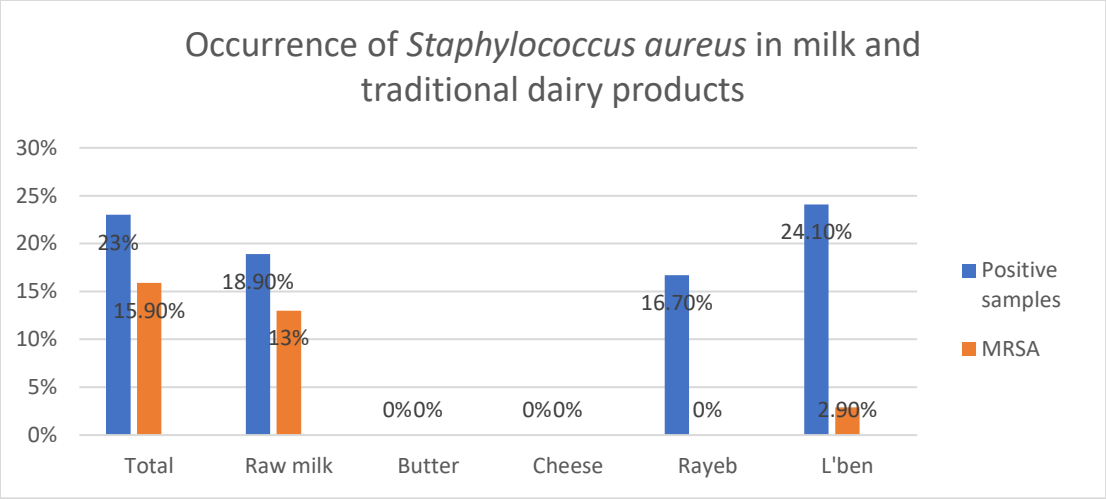

Figure 10: Occurrence of *Staphylococcus aureus* in milk and traditional dairy product (Titouche *et al.*, 2019)

None of the MRSA strains carried the PLV (*lukF*/S-PV) gene, they all belonged to the same *spa* type (t024), sequence type (ST8), they harbored the *blaZ* and *tetK* genes and enterotoxin genes, as well as the *scn* gene (immune evasion cluster system), indicating their clonal relationship and epidemiological link.

Which suggests that strains circulating at farms may be found at the end of the dairy chain, but it is difficult to confirm the origin of these strains because the nasal carriage of animals and farmers were not checked.

3.2.4 *Staphylococcus aureus* in sausages (merguez) in Algeria:

In order to determine the prevalence and antibiotic susceptibility of *Staphylococcus aureus* contamination of raw sausage and investigate potential risk factors associated with the occurrence of foodborne poisoning among sausage consumers' behavior, a total of 230 butcheries from ten subdivisions of Algiers were included randomly to collect raw sausage samples and to distribute 700 structured questionnaires to meat consumers. The risk factors were analyzed by studying their association with the occurrence of consumers who claimed to have food poisoning after consuming sausage (Hachemi *et al.*, 2019).

The overall prevalence of *S. aureus* contamination from sausages was 25.22% (n=58/230). Over 83.33% of strains showed resistance to at least one of the antibiotics tested. The most

important was for tetracycline (58%) followed by fosfomycin (33%), penicillin G (25%), and oxacillin (36%).

Out of the 700-questionnaire handed out, 440 responded, 22.16% (n=379) revealed having food poisoning after sausage consumption. The highest prevalence was found in Beraki (68%), Cheraga (44%), and El Harrach (43.75%), also the same cities with the worst sausage quality.

3.3 *Staphylococcus aureus* in small ruminants:

3.3.1 In sheep:

A study by (Azzi *et al*., 2020), aimed to characterize *S. aureus* isolated from milk samples of sheep with clinical mastitis in Medea province, Algeria. By investigating the antimicrobial susceptibility, the distribution of resistance genes and the genetic diversity of isolates.

In this study, 252 samples of clinical mastitis cases were collected in three district departments (Ain-boucif, Chahbounia and Chellalet-Eladhaoura) in the south of Medea, which were characterized by an intensity of sheep farming.

One hundred twenty-one Staphylococci were isolated from a total number of 252 milk samples of sheep mastitis cases (51.93%). Out of these, (57.02%) were identified as *Staphylococcus aureus*. 27 (10.71%) milk samples were negative and 8 (3.17%) were considered as contaminated for containing more than three bacterial types.

Antimicrobial susceptibility testing revealed that 68.12% of all isolates were resistant to one or more antibiotics. The results of the present study show a high frequency of tetracycline and penicillin resistance.

Various spa types were observed among *S. aureus* isolates (14 different spa types), in which the spa type t1773 was the most predominant (43/69 isolates; 62.32%). One Multi-Drug resistant strain (MDR) belonging to t359 type was isolated.

Therefore, sheep milk might present a significant risk of dissemination of resistant *Staphylococcus* to consumers, especially for milk intended for family consumption and generally does not undergo any thermal processing. Also, the high frequency of resistant strains poses a problem when choosing the mastitis treatment protocol.

3.3.2 In goats:

This study by (Gabli *et al.*, 2019) aimed to determine the prevalence and the causative bacteria of mastitis in dairy goat farms in the four Eastern Algeria region.

Conducted on 845 local dairy goats, aged 2-6 years, between the 2nd and 6th months of their lactation, free from brucellosis and not subject to any antibiotic treatment at sampling, from January 2015 to March 2018. The number of goats examined varied from 30 to 60 lactating goats per farm.

Infection was present in 16/18 farms (88.88%), and 2/18 farms (11.11%) were free of intramammary infection.

Thirty-two bacteria were isolated from the samples (32 milk samples collected from 30 goats with clinical mastitis). *Staphylococcus aureus* was the predominant species 30/32 (93.75%) of the samples. The total frequency of the four regions was 3.55% (30/845).

California mastitis test (CMT) was performed on 815/845 healthy presumed goats belonging to 18 farms, 46 goats (5.64%) had Subclinical Mastitis (SCM). The results of the bacteriological analyses revealed 79 bacterial species distributed in 10 different bacterial species with a predominance of *S. aureus* with 32(40.50%).

S. aureus was most isolated from clinical mastitis cases that recorded a frequency of 39.24% (31/79), whereas Coagulase-Negative Staphs (CNS) were most commonly found in SCM cases with a frequency of 60.76% (48/79).

3.4 *Staphylococcus aureus* in cattle breeding:

To assess the prevalence of *S. aureus* in raw milk in dairies, to study the effect of seasons on the contamination of milk and the susceptibility of isolated strains to antibiotics, and to estimate the risk on the health consumer, (Matallah *et al.*, 2019) used the ISO method 6888-1 for *Staphylococcus* screening. Antimicrobial susceptibility to the 11 most used antibiotics in veterinary medicine was assessed using the disk diffusion assay.

The study was carried out in three different dairies, 301 samples were collected at three processing steps, 244 samples of raw milk from cisterns of different collectors MCC, 22 from the mixing tank of different milks before pasteurization MTMBP, and 35 from milk tank after

pasteurization (TMP). The samples were collected during the four seasons of this year, 112 in spring, 60 in summer, 57 in fall, and 72 in winter.

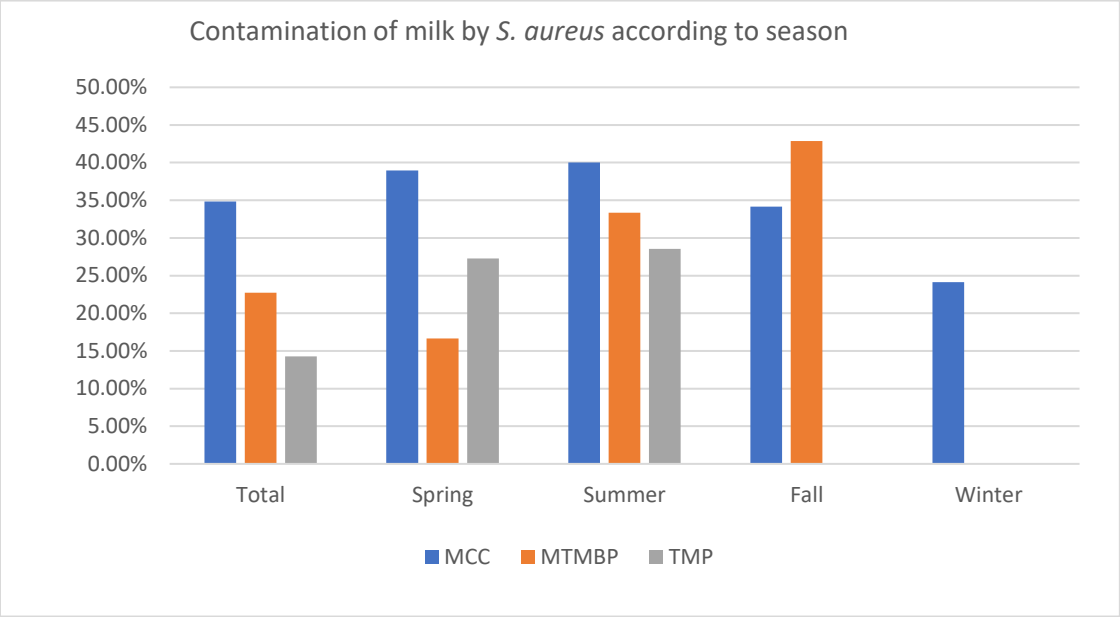

Figure 11: Contamination of dairy milk by *S. aureus* according to season (Matallah *et al.*, 2019)

47.36% of isolates had resistance to a single antibiotic, 4.21% to two antibiotics, and 3.15% to several antibiotics. 49.47% of the strains were resistant to penicillin and 5.26% to tetracycline. Two strains isolated in the same collector, isolated in two different seasons (summer and winter) had multiple resistance for the same antibiotics (tetracycline, erythromycin, clindamycin, and penicillin), this is due to the persistence of these resistant strains in a poorly washed material or in the udder after poorly treated mastitis.

4 Surveillance of the Health Hazard linked to *S. aureus* in Algeria:

As a tool for the prevention and management of health risks, surveillance is a systematic and continuous method aimed at collecting, validating and analyzing health information of interest and disseminating it within deadlines compatible with the implementation of measures. required (WHO, 2019).

The role of the Services Department is to implement and ensure the application of legislative and regulatory provisions in the field of animal health and veterinary public health. The DSV also collaborates with other ministries within the framework of a multidisciplinary approach. The main objective of our study is to take stock of the national and international strategies initiated by, or involving, the Algerian veterinary services as part of the surveillance of the health hazard linked to *Staphylococcus aureus* in Algeria: programs involved in the antibiotic resistance and food safety.

4.1 National programs:

The state is the guarantor of the organization of an efficient health system. First of all, through the establishment and sufficient funding of centralized human health and animal health organizations: through the Ministry of Health and the Ministry of Agriculture and Fisheries. In a "One Health" approach, the two ministries should be intimately linked. Then by the organization of health services throughout their territory: hospitals and medical practices in human health, veterinary services and veterinary practices in veterinary medicine.

4.1.1 Food security management:

Food safety must be considered. It is linked to efficient veterinary services throughout the life of the animal. The external determinants of health must also be considered by governments. Among them, transport systems, trade, immigration, or the environment.

In the event of food-borne outbreaks, veterinarians play a key role in traceability investigations aimed at tracing back to the farm of origin, as well as in the design and implementation of corrective measures once the source identified. It is essentially the veterinarian working in the hygiene offices who is responsible for this mission in the event of a declaration of an outbreak of TIAC. The veterinarians of the public hygiene office must work in close collaboration with

other professional categories and stakeholders, in particular human and environmental health professionals, epidemiologists.

4.1.2 Organization of Algerian Veterinary Services:

The Directorate of Veterinary Services under the supervision of the Ministry of Agriculture and Rural Development acts in the field of the protection of animal health, in application of the law n ° 88-08 of 26/01/1988, relating to veterinary medicine and animal health protection. As such, its mission is, in particular, to implement and ensure the application of legislative and regulatory provisions in the field of animal health and veterinary public health.

At the local level, the veterinary services are represented by a Wilaya Veterinary Inspection (IVW) positioned at the level of the Directorate of Agricultural Services (DSA). It is under the authority of a wilaya veterinary inspector. The Wilaya Veterinary Inspectorate is assisted by: The veterinarian in charge of the epidemiological surveillance network, the veterinarian responsible for food hygiene, and the veterinarian responsible for pharmacovigilance. Under the authority of the wilaya veterinary inspector, there are other veterinary posts such as: - Veterinarians at border posts, Veterinarians at slaughterhouses, Veterinarians at the hygiene offices and Subdivisions, and Private veterinarians.

4.1.3 The veterinarians of the municipality:

Interministerial Instruction between the Ministry of Agriculture and the Ministry of the Interior number 421 / SIM, relating to the assignments and activation of veterinary doctors from the Ministry of Agriculture at the level of municipal health offices and defines their role and fields of intervention of veterinarians of the municipal hygiene office as follows:

- Inventory, control and monitoring of establishments of all kinds handling animal products (restaurants, canteens, etc.).
- Census, control and monitoring of all storage places for animal and fishery products,
- Control of the sanitary quality of foodstuffs (fresh, frozen, deep-frozen or canned animal products) and placed on the market for consumption,
- Control of communicable diseases and their vectors,

- Control of the sanitary quality of products intended for animal consumption or level of storage (raw material) of production (finished products) and distribution,
- Control at the level of the cattle markets, - Technical approval for the establishment of the various buildings for breeding, slaughtering, processing and / or storage of animal products,
- Intervention in the context of environmental pollution,
- Participation with the doctor in health education at municipal level.

4.1.4 Multisectoral Antimicrobial Resistance Committee:

Algeria had a legal framework (n ° 17-310) relating to the creation, missions, organization and functioning of the multisectoral committee for the fight against antimicrobial resistance.

4.1.5 Algerian PASCRA Program Monitoring Contaminants Food Residues:

The Ministry of Agriculture, Rural Development and Fisheries, through its Directorate of Veterinary Services, launched in 2012, a control and monitoring plan for residues in food of animal origin and animal feed, referred to as the **PASCRA** plan. This plan is an essential tool for:

- The detection of a contaminant or the monitoring of contamination levels, on a regular and prolonged basis in foods of animal origin
- Carry out analyzes on a sample, selected from a target population in order to implement actions (sanctions management measures)

Contaminants concerned: veterinary drugs, anabolic substances, heavy metals, microbiological contaminants

Target population: live animals and food products of animal origin, at different stages of the production chain.

4.2 International programs:

Governments, through the ministries of health and agriculture, and veterinary services, are responsible for the surveillance and control of diseases in their territory. Globalization results in a flow of people, animals and goods across borders, and highlights the inability of governments to act alone on the determinants of health. Their sole action, without international cooperation, cannot guarantee the health status of individuals in their country. Governments

must therefore adopt transnational strategies, with the governments of border countries but also international associations.

Algeria has embarked on the path of international coordination of control systems relating to animal and human health and food safety on the global legal basis of the notification of animal and human diseases. Diseases must be the subject of immediate and transparent notification. The notification allows for the rapid dissemination of information on animal diseases, including zoonoses

4.2.1 International Cooperation:

The OIE, FAO and WHO are working together to set up intersectoral mechanisms to carry out risk assessments during outbreaks of foodborne illness or other crisis situations affecting health security.

- INFOSAN - FAO / WHO International Network of Food Safety Authorities.
- GLEWS + FAO / OIE / WHO Early Warning and Rapid Response System for major animal diseases transmissible to humans.
- EMPRES Food Safety - Part of FAO's Prevention and Rapid Response System
- GLASS International Antimicrobial Resistance Surveillance System.

4.2.2 GLASS International Antimicrobial Resistance Surveillance System:

WHO has a Global Network for the Surveillance of Bacterial Resistance to Antibiotics, of which Algeria is a member. This GLASS surveillance system was launched to support a standardized approach to collecting, analyzing and reporting antimicrobial resistance data globally, to support decision making, motivate local actions, national and regional, and provide the evidence base for action and advocacy.

Algeria transmits epidemiological information to WHO as part of international collaboration through a GLASS-AARN network collaboration: Algerian Antimicrobial Resistance Surveillance Network.

The Algerian network monitoring of antimicrobial resistance (Algerian Antimicrobial Resistance Network) AARN launched Bacteriological Laboratory Medical and resistance to antibiotics monitoring of the Institute Pasteur in 2015 (IPA), was responsible for monitoring antibiotic

resistance in humans and animals (IPA, 2015). The two axes are now separate and we have not been able to obtain any additional information on this network activity since the official site www.sante.dz/aarn is no longer hosted.

No activity report of this network has been put online since its creation in 2015, which testifies to the lack of communication of data relating to antimicrobial resistance at the national level whereas it is recommended by the GLASS network, of which Algeria and AARN are members.

WHO encourages GLASSS member countries to strengthen the platform's capacity to be linked to other antimicrobial resistance surveillance systems, including in the areas of animal health (WHO, 2016).

During the initial implementation of the GLASS system, the results of susceptibility testing samples to test antimicrobial will be classified according to the guidelines of the Clinical and Laboratory Standards Institute (CLSI).

5 Conclusion:

MRSA isolates remain a worldwide public health problem and have been reported from both hospital and non-hospital reservoirs, with the appearance of community associated MRSA (CA-MRSA) then Livestock associated MRSA (LA-MRSA) mainly belonging to clonal complex (CC)398 in cows and sheep as apparent host, but has ever since been reported from chicken, turkey, veal calves, cows, horses and dogs. It is thus noteworthy that LA-MRSA isolates do not seem to respect the species barrier as opposed to other *S. aureus* lineages.

In Algeria, the main studies on MRSA have been published from hospital settings, with data confirming the predominance of the PVL-positive European CA-MRSA (ST80-IV-pos) clone, in both community and health-care settings.

The data also suggests a high prevalence and a wild diffusion of toxinogenic *S. aureus* isolates, the detection of Clonal Complexes specific to animals in humans (CC97, CC130, CC133, ST398 and ST705) indicates the ability to cross the species barrier and jump between humans and several animal species, support the hypothesis that animals are potent reservoirs of multidrug-resistant and toxinogenic bacteria.

Our synthesis also revealed a high prevalence of PVL+ MRSA strains in food, which is to be expected, as protein-rich foods are known to harbor *S. aureus,* and are associated with food poisoning. But it is also due to insufficient hygienic and sanitary practices.

Staphylococcus aureus is a main cause for mastitis in sheep, goats and cattle. It was recorded in most mastitis cases in these animals, provoking Subclinical Mastitis (SCM), and highly disseminated in milk, which present a significant risk for family consumption, as it does not generally undergo thermal treatment.

All *S. aureus* strains isolated in the studies above, represents a high multidrug resistance, especially to penicillin, oxacillin, tetracycline and erythromycin, Vancomycin was the most effective against MRSA, the presence of residues of these antibiotics in food products is an indicator of poor hygiene, and may be suggestive of the extent of misuse of antibiotics in medical and veterinary practices in Algeria.

The results provided by these studies are quite alarming, animals are potent reservoirs of this multidrug-resistant and toxinogenic bacteria, the risk of transmission of *S. aureus* and MRSA carrying different antimicrobial resistance and virulence genes such as *pvl* and *tsst* genes cannot be ignored.

In order to fight this situation, the Algerian government, in cooperation with the World Health Organization, passed laws to combat the random practices by some doctors and veterinarians, as well as hygiene and sanitary control in establishments handling food products of animal origin (restaurants, canteens, etc.). The veterinary services are in charge of the epidemiological surveillance, food hygiene, pharmacovigilance, and sanitary control in slaughterhouses, butcheries, meat selling centers and fisheries.

It also launched a control and monitoring plan for residues in food of animal origin and animal feed, **PASCRA** plan, for the detection of contaminants such as antibiotic residues, or the monitoring of contamination levels in live animals and food products of animal origin, at different stages of the production chain.

Algeria also collaborate with WHO through a GLASS-AARN network collaboration: Algerian Antimicrobial Resistance Surveillance Network AARN in 2015. Unfortunately, no activity report of this network has been put online since its creation, which testifies to the lack of communication of data relating to antimicrobial resistance at the national level.

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Annexes:

Executive Decree No. 17-310 of 4 Safar 1439 corresponding to October 24, 2017 on the creation, missions, organization and functioning of **the national multisectoral committee for the fight against antimicrobial resistance.**

The Prime Minister, On the report of the Minister of Health, Population and Hospital Reform, Having regard to the Constitution, in particular Articles 99-4 ° and 143 (paragraph 2); Considering the law n ° 85-05 of February 16, 1985, modified and supplemented, relating to the protection and the promotion of health; Considering the law n ° 88-08 of January 26, 1988 relating to the activities of veterinary medicine and the protection of animal health; Considering the presidential decree n ° 13-293 of 26 Ramadhan 1434 corresponding to August 4, 2013 publishing the international health regulations (2005), adopted in Geneva, on May 23, 2005; Considering the presidential decree n ° 17-242 of 23 Dhou El Kaâda 1438 corresponding to August 15, 2017 appointing the Prime Minister; Considering the presidential decree n ° 17-243 of 25 Dhou El Kaâda 1438 corresponding to August 17, 2017 appointing members of the Government; Considering the executive decree n ° 11-379 of 25 Dhou El Hidja 1432 corresponding to November 21, 2011 fixing the attributions of the minister of health, population and hospital reform; Decrees:

Article 1. - The purpose of this decree is to create, organize and operate the national multisectoral committee for the fight against antimicrobial resistance, and to set its missions, hereinafter referred to as the National Multisectoral Committee".

Art. 2. - The national multisectoral committee reports to the minister responsible for health.

Art. 3. - The national multisectoral committee is a permanent body for consultation, concertation, coordination, monitoring and evaluation of the activities of the national plan to combat antimicrobial resistance. As such, he is responsible, in particular:

- develop a national plan for combating antimicrobial resistance and determine the mechanisms for its implementation;
- ensure the coordination, monitoring and evaluation of the activities foreseen in the national plan to combat antimicrobial resistance;

- to propose any measure aimed at strengthening the national plan to combat antimicrobial resistance;
- initiate training, information, awareness and communication actions inherent in the fight against antimicrobial resistance;
- to propose any research action related to its missions.

Art. 4. - The health sector is the national focal point in the fight against antimicrobial resistance.

Art. 5. - The national multisectoral committee, chaired by the minister responsible for health or his representative, is composed as follows:

Under the central administration of the Ministry of Health, Population and Hospital Reform: * a representative, general directorates responsible for: - prevention and health promotion; - health services and hospital reform; - pharmacy and health equipment. 2. For the ministries: * a representative of the following sectors: - the ministry of national defense; - the ministry responsible for the interior, local communities and regional planning; - the ministry in charge of finance; - the ministry in charge of national education; - the ministry responsible for higher education and scientific research; - the ministry in charge of industry and mines; - the ministry in charge of agriculture, rural development and fisheries; - the ministry in charge of trade; - the ministry responsible for communication; - the ministry in charge of water resources; - the ministry in charge of labor, employment and social security; - the ministry responsible for the environment and renewable energies. The representatives of the sectors mentioned above carry out their missions within the national multisectoral committee as the focal point of their sector. 3. For public establishments: * a representative of the following public establishments: - the national institute of public health, - the Pasteur institute of Algeria; - the national toxicology center; - the national laboratory for the control of pharmaceutical products; - the national institute of veterinary medicine; - the national plant protection institute; - the Algerian center for quality control and packaging. 4. In respect of personalities: - five (5) personalities recognized for their competence in the fight against antimicrobial resistance, appointed by the Minister responsible for health. The national multisectoral committee can call on any competent person likely to help it in its work.

Art. 6. - The members of the national multisectoral committee are appointed for a term of five (5) years, by order of the Minister in charge of health, on the proposal of the authorities and organizations to which they report. In the event of termination of the mandate of a member of the national multisectoral committee, he is replaced in the same way for the remainder of the mandate.

Art. 7. - The national multisectoral committee meets every three (3) months, in ordinary session, when convened by its president. It can meet in extraordinary session, on convocation of its president or at the request of two thirds (2/3) of its members.

Art. 8. - The agenda of the meetings is established by the president and sent to the members of the national multisectoral committee within fifteen (15) days, at least, before the date of the meeting. This period may be reduced for extraordinary sessions without being less than eight (8) days.

Art. 9. - The national multisectoral committee validly deliberates in the presence of half of its members. In the absence of a quorum, a new meeting is scheduled within eight (8) days of the date of the postponed meeting and the committee deliberates regardless of the number of members present.

Art. 10. - The deliberations of the multisectoral national committee are taken by a majority of the votes of the members present. In the event of a tie vote, that of the president is decisive. The deliberations are recorded in minutes transcribed in a special register, listed and initialed by the president.

Art. 11. - The national multisectoral committee can create technical working groups, whose missions, organization and functioning are fixed by the internal regulations.

Art. 12. - The national multisectoral committee sits at the level of the national public health institute.

Art. 13. - The national multisectoral committee has a secretariat provided by the general directorate in charge of prevention and health promotion.

Art. 14. - The national multisectoral committee draws up and adopts its internal regulations.

Art. 15. - The national multisectoral committee draws up an annual report on its activities. This report is sent to the Minister of Health.

Art. 16. - The operating expenses of the multisectoral national committee are entered in the operating budget of the ministry in charge of health.

Art. 17. - This decree will be published in the Official Journal of the People's Democratic Republic of Algeria. Done in Algiers, 4 Safar 1439 corresponding to October 24, 2017.