Microbiology Spectrum
American Society for Microbiology Press

Antimicrobial Resistance in *Streptococcus* spp.

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ABSTRACT The genus *Streptococcus* includes Gram-positive organisms shaped in cocci and organized in chains. They are commensals, pathogens, and opportunistic pathogens for humans and animals. Most *Streptococcus* species of veterinary relevance have a specific ecological niche, such as *S. uberis*, which is almost exclusively an environmental pathogen causing bovine mastitis. In contrast, *S. suis* can be considered as a true zoonotic pathogen, causing specific diseases in humans after contact with infected animals or derived food products. Finally, *Streptococcus* species such as *S. agalactiae* can be sporadically zoonotic, even though they are pathogens of both humans and animals independently. For clarification, a short taxonomical overview will be given here to highlight the diversity of streptococci that infect animals. Several families of antibiotics are used to treat animals for streptococcal infections. First-line treatments are penicillins (alone or in combination with aminoglycosides), macrolides and lincosamides, fluoroquinolones, and tetracyclines. Because of the selecting role of antibiotics, resistance phenotypes have been reported in streptococci isolated from animals worldwide. Globally, the dynamic of resistance acquisition in streptococci is slower than what is experienced in *Enterobacteriaceae*, probably due to the much more limited horizontal spread of resistance genes. Nonetheless, transposons or integrative and conjugative elements can disseminate resistance determinants among streptococci. Besides providing key elements on the prevalence of resistance in streptococci from animals, this article will also largely consider the mechanisms and molecular epidemiology of the major types of resistance to antimicrobials encountered in the most important streptococcal species in veterinary medicine.

TAXONOMIC OVERVIEW OF STREPTOCOCCI

More than 60 *Streptococcus* species have been recognized so far. Some of these, such as *S. pyogenes*, *S. agalactiae*, *S. equi*, *S. canis*, and *S. iniae*, produce hemolytic factors and, when cultivated on solid media containing blood, can be classified as beta-hemolytic. However, nonhemolytic variants can also be observed (1). Isolates belonging to other species, such as *S. dysgalactiae* subsp. *dysgalactiae*, *S. pneumoniae*, *S. mutans*, *S. salivarius*, *S. sanguinis*, *S. gordonii*, *S. mitis*, and *S. oralis*, produce hydrogen peroxide that partially lyses the erythrocytes, with the subsequent oxidation of the heme group resulting in a greenish pigment in the medium that is often interpreted as alpha-hemolysis. This oxidation process is influenced by several cultivation conditions and is variably evident. For this reason, it is preferable to consider those latter-mentioned species as nonhemolytic. The truly nonhemolytic species, mainly encompassing *S. gallolyticus* (formerly *S. bovis*), were also named gamma-hemolytic. A classification of *Streptococcus* species proposed by Rebecca Lancefield in the 1930s was based on the antigenic reaction of the cell wall-associated carbohydrates and remains classically used (2). On the basis of this approach, streptococci are distributed into groups ranging from A to W, depending on the antibodies recognizing the specific carbohydrates of a definite streptococcal species. Nevertheless, the whole picture is sometimes complicated

Received: 30 January 2017, **Accepted:** 4 January 2018, **Published:** 29 March 2018

Editors: Frank Møller Aarestrup, Technical University of Denmark, Lyngby, Denmark; Stefan Schwarz, Freie Universität Berlin, Berlin, Germany; Jianzhong Shen, China Agricultural University, Beijing, China, and Lina Cavaco, Statens Serum Institute, Copenhagen, Denmark

Citation: Haenni M, Lupo A, Madec J-Y. 2018. Antimicrobial resistance in *Streptococcus* spp. *Microbiol Spectrum* 6(2):ARBA-0008-2017. doi:10.1128/microbiolspec.ARBA-0008-2017.

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by the fact that several antibodies can react with isolates belonging to the same species. For instance, depending on the isolates, *S. dysgalactiae* subsp. *equisimilis* may be classified as belonging to the C or G group, while it may also be classified, even though less commonly, as group A or L (3); isolates from *S. phocae* may belong to either the C or G group; isolates from *S. infantarius* are sporadically considered as group D; isolates from *S. anginosus* are indifferently classified as group A, C, G, F, or N; isolates from *S. constellatus* subsp. *constellatus* belong to either group F or N; sporadic isolates belonging to *S. constellatus* subsp. *pharyngis* can be considered as group C; isolates from the *S. intermedius* species can be considered as group N; and finally, isolates belonging to *S. porcinus* are classified in either group P, U, or V.

In the following sections, the most relevant *Streptococcus* species responsible for diseases in animals and/or humans will be summarized. The relative resistances to selected antibiotics will be discussed in the sections on macrolides-lincosamides-streptogramins B tetracyclines, beta-lactam resistance, fluoroquinolone resistance, and integrative and conjugative elements (ICEs).

Group A

Streptococci have diverse ecological origins, and certain species are exclusively adapted to a unique host as exemplified by the beta-hemolytic *S. pyogenes*, which is considered as the most pathogenic type of streptococcus for humans, together with *S. pneumoniae*, and is responsible for pharyngitis, erysipelas, and other invasive diseases such as soft tissue infection, rheumatic fever, glomerulonephritis, and streptococcal toxic shock syndrome (STSS) (4, 5). The finding of *S. pyogenes* in animals has been debated. According to Copperman (6), pets could have been the source of contagious pharyngitis (6), but no expansion of these findings has been reported, supporting the hypothesis that humans are the exclusive reservoir of *S. pyogenes*.

Group B

The beta-hemolytic *S. agalactiae*, or group B streptococci, according to the Lancefield's classification, is a commensal of the human intestinal and urogenital tract and is infamous as a human pathogen causing severe diseases such as pneumonia, sepsis, and meningitis in newborns and pregnant women; recently, its pathogenic importance in elderly and immunocompromised patients has been re-evaluated (7). *S. agalactiae* is also an animal pathogen and has been reported from a variety of hosts such as fish with meningoencephalitis (8), camels with mastitis and joints infections (9), and horses with unspecified disease or death (10). Classically, *S. agalactiae* has been associated with mastitis in cows (11), and the zoonotic potential of *S. agalactiae* is debated. On one side, genomic comparative approaches highlight a specific host adaptation of *S. agalactiae* isolates causing infections (12); on the other side, infections of humans from consumption of fish infected by *S. agalactiae* has recently been documented (13). Also, experimental infections of fish with *S. agalactiae* isolates of human origin have resulted in fish death (14). Globally, the hygienic control measures implemented for controlling contagious bovine mastitis have contributed to a sharply decreased prevalence of *S. agalactiae* in the veterinary sector (15, 16).

Group D

Group D streptococci were divided into two diverging groups in the early 1980s: *S. feacalis* and *S. faecium*, which were renamed *Enterococcus faecalis* and *Enterococcus faecium* (17). Since then, several new species have been added to the *Enterococcus* genus (18), which will not be discussed in this review.

Formerly, *S. bovis* was included in the viridans group of streptococci, and its taxonomy has been reviewed in several studies. Overall, several previously identified *S. bovis* isolates were classified as group D according to Lancefield's reaction, as shown in Table 1. Molecular evidence has provided the basis for the classification of the former *S. bovis* isolates into five species: *S. gallolyticus* subsp. *gallolyticus*, *S. gallolyticus* subsp. *pasteurianus*, *S. gallolyticus* subsp. *macedonicus*, *S. infantarius* subsp. *infantarius*, and *S. lutetiensis* (19). Isolates belonging to *S. gallolyticus* subsp. *gallolyticus* have been found as commensals of the gastrointestinal tract of humans and animals but also cause invasive diseases such as sepsis, endocarditis, arthritis, and meningitis in both humans and animals (Table 1). The transmission of *S. gallolyticus* subsp. *gallolyticus* between animals and humans has been reported (20), highlighting the zoonotic potential of this species. *S. gallolyticus* subsp. *pasteurianus* is an emergent infective agent in human medicine that is responsible for sepsis, bone and joint infections, and meningitis (21–23). In birds, this bacterium is responsible for similar diseases (24, 25). *S. lutetiensis* has rarely been associated with infective endocarditis and sepsis (26).

Group E

In Lancefield's group E, *S. porcinus* is typically associated with sepsis, endocarditis, pneumonia, and lymphadenitis in swine (27). Infections sustained by *S. porcinus*

TABLE 1 Overview of streptococci causative of infections in humans and animals[a]

Lancefield group	Hemolysin	Species	Host	Associated disease	References
B	Beta	*S. agalactiae*	Human	Sepsis, meningitis, pneumonia, joint and urinary tract infections	7, 11, 199, 200
			Cows, camels, horses, dolphins, fish	Mastitis, joint infection, meningitis, death	
C	Alpha	*S. dysgalactiae* subsp. *dysgalactiae*	Humans	Endocarditis, joint infection, cellulitis	48, 201, 202
			Fish, cows	Tissue necrosis, mastitis	
	Beta	*S. dysgalactiae* subsp. *equisimilis*	Humans	STSS, sepsis, soft tissue infections, pneumonia, pharyngitis	33, 203–210
			Swine, seals, horses	Arthritis, endocarditis, lymphadenitis, joint infection, strangles-like disease, respiratory tract infection	
	Beta	*S. equi* subsp. *equi*	Horses	Strangles disease	32
	Beta	*S. equi* subsp. *zooepidemicus*	Humans	Nephritis, STSS	33
			Sheep, horses	Mastitis, lymphadenitis, joint and respiratory infections, endometritis	31, 32, 211
	Beta	*S. phocae*	Fish, seals	Respiratory infections, abortions, sepsis	212
D		*S. gallolyticus* spp. *gallolyticus*	Humans	Sepsis, endocarditis, arthritis, meningitis	213–216
			Koalas, birds	Intestinal colonizer, endocarditis, sepsis	
		S. gallolyticus spp. *pasteurianus*	Humans	Sepsis, bone and joint infections, meningitis	21–25
			Birds	Sepsis, meningitis	
E	Beta	*S. porcinus*	Humans	Urinary tract, placenta, and wound infections, sepsis	27, 28, 217, 218
			Swine	Endocarditis, respiratory tract infection, sepsis	
G	Beta	*S. canis*	Humans	Skin, soft-tissue and respiratory infections, sepsis	34, 35, 219, 220
			Dogs, cats	Skin, soft-tissue, and urinary tract infections, otitis, arthritis, STSS	
R	Nonhemolytic/ beta	*S. suis*	Humans	Sepsis, meningitis, endocarditis, STSS	37, 221–225
			Swine, boars, rabbits	Sepsis, meningitis, pneumonia, arthritis	
Undefined	Beta	*S. iniae*	Humans	Soft-tissue infection	48, 49
			Dolphins, fish	Abscess, streptococcosis, sepsis	226–231
		S. uberis/S. parauberis	Cows, horses	Mastitis	11, 16, 30, 43

[a]Isolates belonging to *S. dysgalactiae* subsp. *equisimilis* react with antigen G with comparable prevalence of antigen C reaction, whereas reaction with antigens A and L are less common; isolates belonging to *S. phocae* react also with antigen G; isolates belonging to *S. porcinus* react also with antigens P, U, and V. Nonhemolytic variant can be recovered among isolates of *S. agalactiae* and *S. dysgalactiae* subsp. *equisimilis*.

have also occurred in humans (28); however, *S. porcinus* isolates infecting humans seem to have a different origin when compared to *S. porcinus* isolates of nonhuman sources (29).

Groups C and G

S. dysgalactiae subsp. *dysgalactiae* belongs to Lancefield's group C and G and plays a major role in mastitis (30). On rare occasions, it has also been found in necrotic tissues of fish and in humans, as responsible for various diseases (Table 1). In the same Lancefield's groups, *S. dysgalactiae* subsp. *equisimilis* is a beta-hemolytic bacterium found associated with strangles-like diseases in horses and with arthritis and endocarditis in swine. Unfortunately, this species is also associated with invasive diseases in humans, such as STSS and sepsis (Table 1). *S. equi* subsp. *zooepidemicus* organisms react with group C and G Lancefield's antigens as well. This organism is commonly found in bovine mastitis (90, 94, 137; also see Table and Table 3) and has sporadically been found associated with mastitis in sheep (31) and is most prevalent in equine infective diseases as the causative agent of joint and respiratory tract infections (32). This species also causes severe infections in humans in association with the consumption of contaminated dairy products (33). Transmission of *S. canis* isolates belonging to Lancefield's

group C and G between pets and humans seems conceivable (34). This bacterium is responsible for arthritis in cats and humans (35) and endocarditis and skin, soft tissue, and urinary tract infections in dogs and humans. Skin lesions seem to represent the entry portal for establishing infections in humans (34, 36). In contrast, *S. equi* subsp. *equi*, belonging to Lancefield's groups C and G and responsible for strangles disease in horses, is exclusively animal adapted (32).

Group R

S. suis is a major pathogen for swine and causes meningitis, endocarditis, sepsis, arthritis, and pneumonia. In humans, *S. suis* is mostly responsible for meningitis and STSS. It is a well-recognized zoonotic agent, and indeed, human exposure to swine and swine-derived food products is a risk factor for infection by *S. suis* (37, 38). The production of a capsule seems to have a major role in pathogenesis, and capsular types 2 and 14 are the most prevalent among *S. suis* isolates that cause disease in humans (39).

Non-Lancefield Streptococci

All other streptococci lacking the Lancefield antigens are thus considered non-Lancefield (or nontypable) streptococci. Several are frequently encountered in animals and are detailed below.

S. uberis

If hygienic measures have been effective to control the dissemination of *S. agalactiae*, the same cannot be said for *S. uberis*, which remains a major animal pathogen and a leading cause of mastitis in cattle (15, 16). This nonserotypable organism has an environmental origin, possesses a flexible metabolism, and is almost exclusively adapted to cattle (40). Infections can occur by a variety of strains, which in some cases are able to persist and propagate among different cows within a herd (41, 42). Rarely, it has been responsible for mastitis in heifers, and even more rarely it has been isolated from shrimps (43–45). The control of *S. uberis* propagation is more challenging than that of other *Streptococcus* spp. probably because of its ability, among others, to survive on bedding material (46, 47).

S. iniae

Another nonserotypable species is *S. iniae*, which was primarily isolated from diseased dolphins and was subsequently confirmed as a major fish pathogen and as responsible for soft tissue infections in humans with zoonotic features (Table 1) (48–52).

S. pneumoniae

S. pneumoniae is a major streptococcal pathogen of humans and is responsible for serious infections such as pneumonia and meningitis; reports of infections in animals are extremely rare and concern horses with respiratory tract infections (53). A recent publication also reported *S. pneumoniae*, probably of human origin, in wild and captive chimpanzees (54). The spread of this pathogen due to the migration of infected animals to other communities or the reintroduction into wild populations of formerly captive animals might be a real danger.

Viridans streptococci

These organisms were defined as viridans because of the hemolytic features described above that produce a greenish pigmentation on blood agar, their absence of Lancefield antigens, and their resistance to the chemical compound optochin. Generally, viridans streptococci are implicated in the establishment of dental caries, arthritis, and infective endocarditis in humans (50–52).

Certain *Streptococcus* species, including *S. sobrinus* and *S. mutans*, the first representative of the mutans group; *S. salivarius*, *S. vestibularis*, and *S. infantarius* from the salivarius group; the anginosus group, including *S. anginosus*, *S. constellatus*, and *S. intermedius*; the sanguinus group, including *S. sanguinis*, *S. parasanguinis*, and *S. gordonii*; and most species of the mitis group, including *S. mitis*, *S. oralis*, *S. cristatus*, *S. infantis*, and *S. peroris*, have exclusive human adaptation; others have been found only in animal hosts, such as *S. macacae* from monkeys, *S. ferus* from wild rodents, *S. orisratti* from rats, and *S. hyointestinalis* and *S. hyovaginalis* from swine, with no associated diseases (55–59). Three species of the viridans group, namely *S. sobrinus*, *S. criceti*, and *S. ratti*, have been reported from humans and experimental rats, whereas *S. alactolyticus* has been found in swine, dogs, and humans (56, 60, 61); *S. downei* was isolated first from a monkey and more recently from human dental plaque (62, 63). Another species of the viridans group, *S. pluranimalium*, has been reported rarely. It was first reported in 1999 from bovine mastitis, and few clinical human cases have been reported since then (64, 65).

This brief introduction does not pretend to be exhaustive. The reviews by Póntigo et al. and Facklam provide a comprehensive nomenclature and classification of streptococci based on molecular and phenotypic features, respectively (1, 66).

EVOLUTION OF ANTIMICROBIAL RESISTANCE IN VETERINARY STREPTOCOCCI

Monitoring Programs

Prevalence data on antimicrobial resistance were principally obtained through dedicated studies performed at the scale of a region, a country, or a consortium of countries. However, only monitoring programs can give an evolutionary picture of antimicrobial resistance rates over time. Consequently, surveillance systems are highly valuable to follow trends and detect emergent resistant phenotypes.

Several national surveillance and monitoring programs in veterinary medicine exist in Europe (67), including the Monitoring of Antimicrobial Resistance and Antibiotic Usage in Animals in the Netherlands program, the Swedish Veterinary Antimicrobial Resistance Monitoring program (SVARM), the Danish Integrated Antimicrobial Resistance Monitoring and Research Program, the German Resistance Monitoring in Veterinary Medicine program, and the French surveillance network for antimicrobial resistance in pathogenic bacteria of animal origin (RESAPATH). Two similar programs cover the North American continent, the National Antimicrobial Resistance Monitoring System for Enteric Bacteria in the United States and the Canadian Integrated Program for Antimicrobial Resistance Surveillance, and one reports Japanese data (the Japanese Veterinary Antimicrobial Resistance Monitoring program). An additional industry-based pan-European monitoring program commissioned by the Executive Animal Health Study Center investigates pathogens from farm (VetPath) and companion animals (ComPath). In addition to the recurrently criticized lack of harmonization (67, 68), a major feature of most programs is their main focus on bacteria of animal origin but of relevance for human health, such as zoonotics and commensal indicators. Accordingly, streptococci of animal origin were poorly included, and data on their resistance to antimicrobials remain limited at a global scale. Indeed, only two monitoring programs reported data on a long-term basis: the Monitoring of Antimicrobial Resistance and Antibiotic Usage in Animals in the Netherlands program from 2002 to 2008 and RESAPATH from 2006 until today. Other programs such as the Swedish Veterinary Antimicrobial Resistance Monitoring program (in 2002), the German Resistance Monitoring in Veterinary Medicine program, and ComPath/VetPath have also documented antimicrobial resistance in streptococci, but on a sporadic basis.

Different Methodologies to Determine Antibiotic Resistance

Standard surveillance programs rely on phenotypic methods that are used in routine diagnostic laboratories. The most frequently used methods are antibiograms performed by disc diffusion and MIC performed by broth microdilution. These techniques generate qualitative or quantitative results, respectively, that are then interpreted according to official guidelines (EUCAST, CLSI, Antibiogram Committee of the French Microbiology Society (CA-SFM), etc.) so that the studied isolates can be classified as susceptible, intermediate, or resistant to the tested antibiotics. In the surveillance systems, the genotypic techniques are only optionally implemented as a second-line characterization.

This traditional approach may be disrupted by the democratization of next-generation sequencing methodologies. Recently, several publications proved the usefulness of large-scale genomic analyses for the efficient detection of resistance mechanisms and capsular types (69), for the sequence-based prediction of beta-lactam resistance using the penicillin-binding protein (PBP) transpeptidase signatures (70), and for the prediction of the antimicrobial profile and its potential evolution toward resistance over time (71). This is, of course, not an exhaustive list of publications using next-generation sequencing, especially in a field that is progressing very rapidly. There are still a couple of drawbacks to the direct implementation of next-generation sequencing in diagnostic laboratories, including the time needed to generate results (which exceeds the 48 hours traditionally needed for phenotypic testing) and the price. However, this methodology is so powerful that it will undoubtedly be used in monitoring programs, at least for long-term surveillance purposes.

Evolution of Resistance in *Streptococcus* spp.

The main *Streptococcus* species studied through monitoring programs were *S. uberis* and *S. dysgalactiae* isolated from bovine mastitis. *S. agalactiae* is also still considered a major streptococcal pathogen associated with bovine subclinical and mild to moderate clinical mastitis, but its incidence has drastically fallen in the past 20 years due to hygiene measures and guidelines for good practices. Consequently, *S. agalactiae* is now only rarely isolated from cattle mastitis, and the numbers are too small to be reliably reported. The evolution of antimicrobial resistance thus focuses on *S. uberis* and *S. dysgalactiae*. Here, we review data on resistance to the main antibiotics used in the treatment of animal infections due to *S. uberis* and *S. dysgalactiae*, i.e., penicillin G, tetracyclines, erythromycin, lincomycin, enrofloxacin, and streptomycin.

Evolution of Antimicrobial Resistance in the Netherlands

The Monitoring of Antimicrobial Resistance and Antibiotic Usage in Animals in the Netherlands program reported antimicrobial resistance data on streptococci isolates collected from milk in the context of intramammary infections, but the monitoring of these pathogens stopped in 2008. From 2002 to 2008, the overall prevalence of resistance was quite stable for most antibiotics, with a seemingly upward trend for a few (72). Resistance to beta-lactams (represented by penicillin G and cefalotin) was only detected in rare cases of *S. uberis* and was absent in *S. dysgalactiae*. The highest rates of resistance were for tetracyclines (around 40% for *S. uberis* and 70% for *S. dysgalactiae*) and lincomycin (also around 40% for *S. uberis* and 25% for *S. dysgalactiae*). The discrepancy between the prevalence of tetracycline resistance in *S. dysgalactiae* compared to *S. uberis* is in accordance with what has been reported in other monitoring programs (see below) and numerous studies (see "Prevalence of Resistance to Macrolides among Streptococci of Bovine Origin" below). Resistance to erythromycin (around 20% for *S. uberis* and 10% for *S. dysgalactiae*) was systematically lower than for lincomycin, suggesting a significant prevalence of non-*erm*-mediated mechanisms of resistance.

RESAPATH, the Ongoing French Monitoring Program

RESAPATH is the only ongoing and long-term monitoring program for, among other topics, resistance to antimicrobials in streptococci in Europe. For *S. uberis*, from 2006 to 2015, antimicrobial resistance was tested on 600 to 1,500 isolates, depending on the nature of the antibiotics, and the global trend was quite stable for all antibiotics (Fig. 1). The highest prevalence of resistance was observed for enrofloxacin, which may be explained by the intrinsic low-level resistance of streptococci to fluoroquinolones. Indeed, in the RESAPATH network, resistance is defined as the addition of both resistant and intermediate phenotypes, which may lead to the overestimation of the prevalence of resistance in the case of fluoroquinolones. For erythromycin and lincomycin, the resistance rates decreased from 24% to 17% between 2006 and 2007, were stable during next 6 years until 2013, and increased again in 2014 to 2015 up to around 22% of resistant isolates. Both curves matched perfectly, indicating a cross-resistance to macrolides-lincosamides involving *erm* genes (see "Resistance to Macrolides, Lincosamides, and Streptogramin B" below). Tetracycline resistance is following a very slow upward trend (from 14% in 2006 to 21% in 2015), to be confirmed in the coming years. Finally, streptomycin is the antibiotic presenting the lowest prevalence of resistance (from 11 to 16% over the 10-year period of 2006 to 2015), albeit the highest among resistance to aminoglycosides. Indeed, rates of resistance to kanamycin and gentamicin only reached 5% and 3%, respectively, in 2015. However, these resistances are of major importance since they may result in the loss of synergy between aminoglycosides and beta-lactams, which is a frequently used combination in veterinary practice. Taken together, these data show globally high basal levels of resistance of streptococci to antimicrobials in 2006 and a slight but increasing prevalence, which will have to be monitored in the near future.

The number of *S. dysgalactiae* isolates that can be considered for global trends in prevalence is around 10 times lower than for *S. uberis* (25 compared to 235 isolates), so that the prevalence rates are subject to wider variations. However, the rates observed are different though more stable than for *S. uberis*. The antibiotic with the highest prevalence of resistance by far was tetracyclines. Up to 85% of the *S. dysgalactiae* isolates were resistant to this drug, which is in accordance with what has been reported in other studies (see "Prevalence of Resistance to Macrolides among Streptococci of Bovine Origin" below). Enrofloxacin presents fluctuating resistance rates of around 50%. Finally, erythromycin, lincomycin, and streptomycin present a stable prevalence of around 22%, 12%, and 6%, respectively. The 10% discrepancy between erythromycin and lincomycin resistance rates deserves special attention since it may signal a divergence in the resistance mechanisms involved compared to *S. uberis*.

Though originating from two countries only, these evolution rates constitute a starting point to address the issue of resistance in *Streptococcus* spp. in veterinary medicine. In line with these trends, the next sections will detail the epidemiology and mechanisms of resistance of the antibiotics mentioned above.

RESISTANCE TO MACROLIDES, LINCOSAMIDES, AND STREPTOGRAMIN B

Erythromycin was the first macrolide discovered in 1952 by McGuire as a natural product originating from *Streptomyces erythreus*. The other macrolides were derived from erythromycin by semi-synthesis, and their core unit consists of a lactone ring that can be constituted by 14, 15, and 16 carbon atoms. These molecules are bacteriostatic in staphylococci and bactericidal in

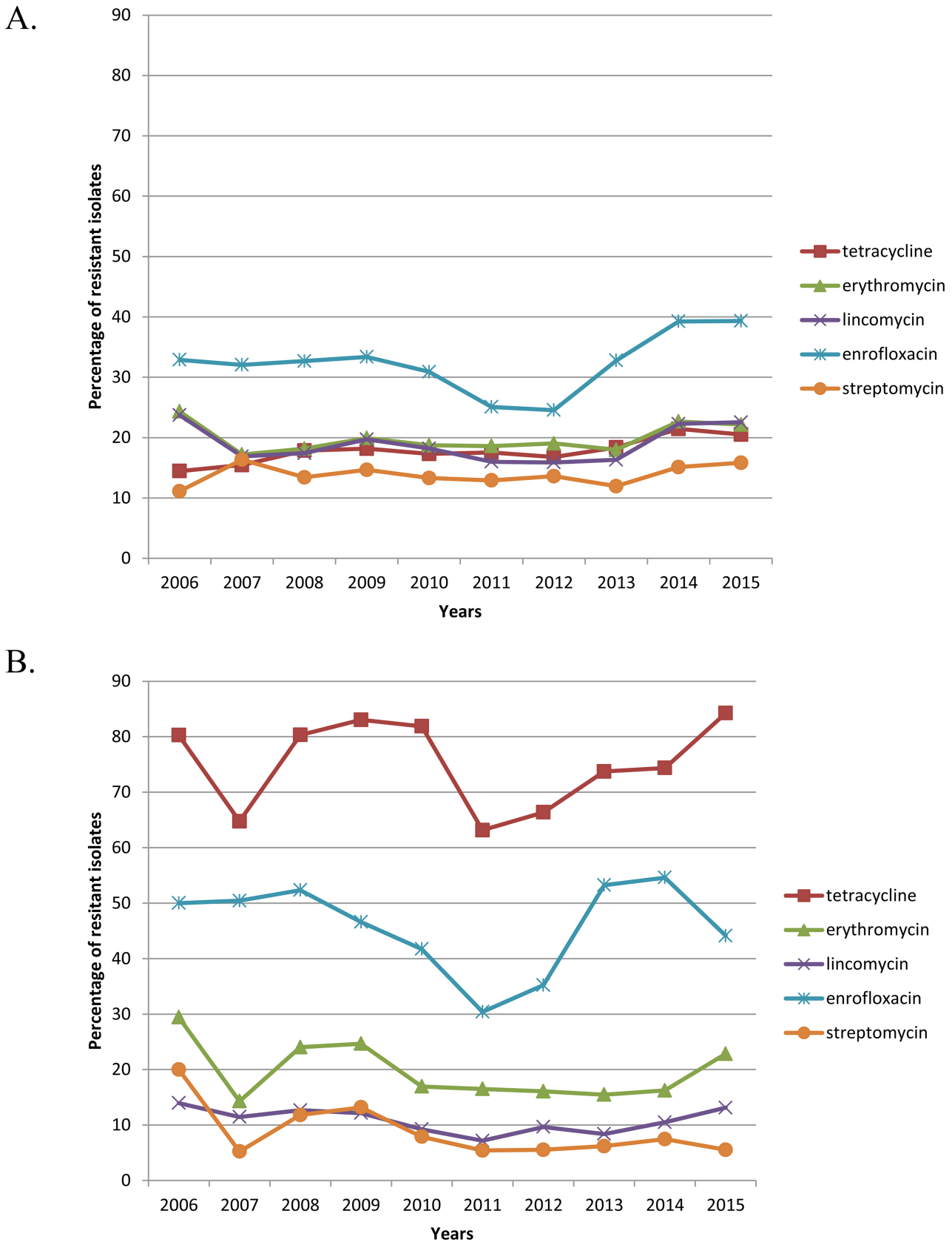

FIGURE 1 Ten-year evolution of resistance in France in (A) *S. uberis* and (B) *S. dysgalactiae*.

streptococci, inhibiting the protein translocation by binding to the 23S or 50S ribosomal subunit at peculiar residues (i.e., the guanine 2505, the uridine 2609, and the adenines 2058, 2059, and 2062) (73). Macrolides have a broad spectrum of action, being effective against Gram-positive and Gram-negative bacteria and intracellular pathogens, and are reputed as valuable agents for their good pharmacodynamics properties, their relatively few side effects, and their good penetration in tissues. Lincosamides, including lincomycin and clindamycin, together with streptogramin B, including pristinamycin and quinupristin, are structurally unrelated to macrolides, but they have a common mechanism of action and, as a consequence, resistance to all these classes of antibiotics is crossed. In addition to the treatment of infections caused by intracellular pathogens, the usage of macrolides and lincosamides in human clinics is principally dedicated to the treatment of uncomplicated infections in patients who are allergic to beta-lactams. In veterinary medicine, macrolides and lincosamides are available as in-feed and injectable formulations and are used for the treatment of a variety of diseases ranging from respiratory tract infections to infective mastitis in food-producing animals, especially swine and cattle (74, 75). Frequently, macrolides and lincosamides are used in combination with other drugs such as aminoglycosides, ampicillin, colistin, tetracyclines, sulfonamides, and trimethoprim (76). Certain macrolides were also used as growth promoters (council regulation EC2821/98, 17 December 1998). Unfortunately, shortly after the introduction of macrolides in human therapy, resistant isolates were recovered; the emergence of resistant isolates has also occurred in animals. In the following subsections we will describe the most common mechanisms of resistance to macrolides, lincosamides, and streptogramins B found in streptococci of animal origin.

Macrolides, Lincosamides, and Streptogramins B Resistance Determinants

Target modification

Ribosomal mutation in the residues crucial to the binding of macrolides results in cross-resistance to all macrolides, lincosamides, and streptogramins B conferring the so-called MLSb phenotype. Human clinical isolates with such mutations have been sporadically observed, probably because this mechanism requires mutations in all the operon copies encoding the ribosomal subunits.

Target protection

The methylation of the adenine at position 2058 is enough to confer an MLSb resistance phenotype. This reaction is mediated by the methylases encoded by the *erm* (erythromycin ribosome methylation) gene family, originated by the natural producers of macrolides. In the presence of an Erm methylase, resistance to lincosamides and streptogramin B can be either constitutive or induced by the presence of erythromycin (73). Overall, this mechanism is the most prevalent method conferring resistance to macrolides in human and veterinary clinical isolates. Currently, about 40 variants of the *erm* gene have been reported, with *erm*(B) gene being the most prevalent (77). It is often located on mobile genetic elements (MGEs) and associated with genes conferring resistance to tetracyclines (see below). These two factors have consistently contributed to the dissemination of resistance to macrolides (78).

Efflux

The second most common mechanism of resistance to macrolides in streptococci is represented by the efflux mediated by the Mef efflux pumps. The *mefA* gene was described for the first time in *S. pyogenes*, and other variants have been reported since then that are principally represented by *mefE* and *mefI* (79). These efflux systems confer resistance to 14- and 15-carbon atom macrolides only, determining an M phenotype. Transcription of *mef* genes is coupled with the expression of *msr* genes encoding for an ATP-dependent efflux system. The presence of *mef* genes seems to be necessary to confer macrolide resistance (80). Genes of the *mef* family are often located on genetic units that can transfer by transformation, such as the MEGA (macrolide efflux genetic assembly) element harboring the *mefE* gene and conjugative transposons such as the Tn*1207.3* harboring the *mefA* variant and the 5216IQ composite element harboring the *mefI* gene (81–83). With a lower prevalence, the *mreA* efflux pump has been reported as well (84). Finally, genes of the *lsa* family have been described, conferring cross-resistance to lincosamides, streptogramin A and pleuromutilins. These genes, encoding ATP-binding proteins, most likely promote the efflux of the antibiotics (192).

Drug modification

Lincosamides can be inactivated by adenylation in position 3 by a 3-lincosamide-*O*-nucleotidyltransferase encoded by the *linB* gene conferring an L phenotype (85). The *linB* gene was first found in a clinical isolate of *E. faecium*. Its origin remains unknown because no similar sequence has been found in natural lincosamide producers. The *linB* gene was reported sporadically; however, its transfer to *S. agalactiae* has occurred

and has been reported from a human clinical isolate in Canada (86). After the first description, the *linB* gene was renamed *lnuB*. Later, Achard et al. unveiled the mechanism behind the lincomycin resistance in an *S. agalactiae* isolate that was surprisingly susceptible to clindamycin. It consisted of a novel nucleotidyltransferase encoded by the *lnuC* gene (87). The LnuD-adenylating clindamycin was later discovered in *S. uberis* (88).

Inactivation of macrolides can also be caused by phosphotransferases encoded by the *mph* gene families with differential affinity for the different macrolide types and lincosamides according to the variant of the *mph* gene expressed (89).

Prevalence of Resistance to Macrolides among Streptococci of Bovine Origin

Studies of the resistance to macrolides in streptococci of bovine origin have focused on isolates responsible for clinical and subclinical mastitis. During an investigation of different streptococcal species from bovine mastitis during 2002 to 2003 in Portugal, Rato et al. found a constitutive MLSb phenotype in 11/60 *S. agalactiae* isolates; among those, 10 isolates were positive for the presence of an *erm*(B) gene and one harbored an *erm*(A) gene (90). Among *S. dysgalactiae* subsp. *dysgalactiae* isolates, 4/18 demonstrated a constitutive MLSb phenotype, with the presence of *erm*(A) and *erm*(B) in 1 and 3 isolates, respectively, whereas all the MLSb-resistant *S. uberis* isolates (8/30) harbored an *erm*(B) gene. An L phenotype was demonstrated in 11 isolates, 3 belonging to *S. dysgalactiae* subsp. *dysgalactiae* and 8 to *S. uberis* species, all of them harboring an *lnuB* gene. In 2005, Duarte et al. found that 8.5% (9/38) of *S. agalactiae* isolates from Brazil were resistant to erythromycin with a constitutive MLSb phenotype. All of the isolates harbored an *erm*(B) and an *mreA* gene; six of these coharbored *erm*(A) and were co-resistant to tetracyclines (29). Contemporaneously, Dogan et al. reported a 3.6% prevalence of erythromycin-resistant isolates among 83 *S. agalactiae* from bovines in New York. The resistance was mediated by Erm(B) in all isolates, and coresistance to tetracyclines was observed as well (91). A study from China was published in 2012 on 55 *S. agalactiae* isolates recovered from bovine mastitis during an undetermined period and reported a 23.5% rate of resistance to erythromycin. All isolates harbored the *erm*(B) gene (92). Pinto et al. analyzed 29 *S. agalactiae* isolates collected between 1980 and 2006 in Brazil. They found that 27% of the isolates were resistant to erythromycin, with *erm*(B) as the most prevalent gene, followed by the *erm*(A) variant. In this study, the presence of a *mef* allele was reported as well (93).

More recently, our investigation of 76 *S. agalactiae* isolates demonstrated an MLSb phenotype in eight isolates, including four isolates with a constitutive phenotype and four with an inducible phenotype. Six isolates harbored an *erm*(B) gene, and the two remaining ones harbored the *erm*(A) variant. In the same study, 4/32 isolates of *S. dysgalactiae* demonstrated the presence of an *erm*(B) gene; in this case also, the constitutive or inducible phenotypes were equally distributed (94). The *erm*(B) gene has also been confirmed as the most common gene conferring resistance to macrolides among *S. dysgalactiae* isolates; for instance, it was present in 4/4 isolates detected in dairy herds in the southwestern United States (95). We conducted a study to characterize the erythromycin resistance of 125 isolates of *S. uberis* collected from bovine mastitis during 2007 to 2008 in France. Overall, 111/125 isolates demonstrated an MLSb phenotype, constitutive in 42.3% of the isolates and inducible in the remaining ones. An *erm*(B) gene was present in all isolates. In this collection, 14 isolates demonstrated an L phenotype and harbored an *lnuB* gene. In one isolate, the less common *lnuD* gene was found as well (96). Contemporaneously, another study, conducted on dairy cows in Mayenne, France, confirmed MLSb resistance in 12 (12/55, 22%) *S. uberis* isolates, which all were positive for the *erm*(B) gene. An *lnuB* gene was present in four isolates with the L phenotype (97). In *S. uberis*, emergence of the *mphB* gene was documented in 2008 (98), but propagation of this mechanism has not occurred in a large scale.

Among others, the German Resistance Monitoring in Veterinary Medicine program has provided extensive data from Germany from 2007 to 2010 (Table 2). Several other studies from different parts of the world and based on the phenotypic characterization of mastitis isolates provided a comprehensive picture of the problematic link to the rise of resistance to macrolides in streptococci causing mastitis. An overview is provided in Table 2, and for exhaustive reports on temporal and geographical evolution of macrolide and lincosamide resistance in streptococci, we suggest the reports from Hendriksen et al. in 2008 and Thomas et al. in 2015 (99, 100). Overall, the lowest prevalence of macrolide and lincosamide resistance was observed in Sweden (101), and large differences in prevalence were observed among countries. However, no major variation was observed from one year to another in a single country.

TABLE 2 Erythromycin and lincosamide resistance in streptococci in animal hosts[a]

Animal host	Country	Year	Bacterial species	No. of isolates	Genetic determinants									Percentage of resistance (%) to		Reference
					mefA	*mefE*	*msr*	*ermA*	*ermB*	*lnuB*	*lnuD*	*mph*	*mreA*	M	L	
Cattle	USA	ND	*S. dysgalactiae*	152										10	25.6	136
			S. uberis	133										9	42.9	
Cattle	France		*S. uberis*	55	0				12	4				22		97
Cattle	USA	ND	*S. dysgalactiae*	4	0	0		0	4					100		95
			S. uberis	20	0	0		0	12					60		
Cattle	China	ND	*S. agalactiae*	55	0			0	13					23.5		92
Cattle	Brazil	1980–2006	*S. agalactiae*	29	5			4	7	0				31	20.7	93
Cattle	France	1984–2008	*S. agalactiae*	76	0			2	6					10.1		94
			S. dysgalactiae	32	0			0	4					ND		
			S. uberis	101	0			0	75	5	1			ND		
Cattle	Brazil	1995–2000	*S. agalactiae*	38	0			6	9	0			9	8.5	8.5	29
Cattle	France	1995–2000	*S. agalactiae*	8										0	0	134
			S. dysgalactiae	41										16.7	11.9	
			S. uberis	50										28	36	
Cattle	Argentina	1999–2003	*S. agalactiae*	36										16.7	19.4	232
			S. dysgalactiae	8										12.5	12.5	
Cattle	USA	2000–2002	*S. agalactiae*	83	0			0	3					3.6		91
Cattle	Portugal	2002–2003	*S. agalactiae*	60	0			1	10	0				18.3	18.3	90
			S. dysgalactiae	18	0			1	3	3				22.2	38.9	
			S. uberis	30	0			0	8	8				26.7	26.7	
Cattle	Sweden	2002–2003	*S. agalactiae*	6										16.7	16.7	133
			S. dysgalactiae	152										0	0.7	
			S. uberis	113										0	0	

Cattle	Korea	2004–2008	*S. agalactiae*	5							0	60	233
			S. bovis group	24							12.5	33.3	
			S. uberis	99							34.3	41.4	
			S. oralis	30							36.7	36.7	
			S. salivarius	13							0	69.2	
			S. intermedius	7							42.8	71.4	
Cattle	Turkey	ND	*S. agalactiae*	5							0	40	169
			S. uberis	18							11	17	
Cattle	France	2007–2008	*S. uberis*	125	0		0	111	3	0	ND	ND	96
Cattle	Estonia	2007–2009	*S. agalactiae*								1.3	6.2	168
			S. dysgalactiae								6.7	7.8	
			S. uberis								8.2	6.6	
Cattle	Germany	2007–2010	*S. agalactiae*	101	2	13	0	15			16.8	ND	234
			S. dysgalactiae	100	2	1	0	10			11	ND	
			S. uberis	102	2	2	0	5			17.6	ND	
Cattle	Switzerland	2010–2012	*S. dysgalactiae*	46							2.2	2.2	238
			S. uberis	208							10.6	10.6	
Cattle	Switzerland	2011–2013	*S. dysgalactiae*	213							ND	37.4	167
			S. uberis	1,228							ND	49.7	
Swine	EU	1987–1997	*S. suis*	404							55.3		139
Swine	Denmark	1989–2002	*S. suis*	103				39			40.8		237
Swine	France	1996–2000	*S. suis*	110							78.2	78.2	235
Swine	Belgium	1999–2000	*S. suis*	87	0			62			71	71	236
Swine	Spain	1999–2001	*S. suis*	151							90.7	87.4	143
Swine	Italy	2003–2007	*S. suis*	57	0			44			81	81	140
Swine	China	2005–2007	*S. suis*	421							67.2	68.4	142
Swine	China	2005–2012	*S. suis*	96	18		0	35	0		38.5	38.5	170
Swine	China	2008–2010	*S. suis*	106	51	51		70			67.9	67.9	146
Swine	Brazil	2009–2010	*S. suis*	260							46.5	84.6	144
Swine	Korea	2010–2013	*S. suis*	227	39			218			94	95.6	104

[a]ND, not determined; M, macrolides; L, lincosamides.

Prevalence of Resistance to Macrolides among Streptococci of Porcine Origin

Macrolides, lincosamides, and streptogramins B are widely used for the treatment of infections in swine. Unfortunately, it appears that the usage of these drugs has influenced the emergence of resistance in *S. suis* (102). High rates of resistance to these drugs were observed over time, ranging from 52% (11/21 isolates) in the first observation in Norway in 1986 (103) to 94% (216/226 isolates) in Korea during 2010 to 2013 (104). The most prevalent genetic determinant is the *erm*(B) gene, whereas *mef*A/E were sporadically detected in human isolates (105). Often, such resistances occur together with tetracycline resistance (see below). *S. suis* may also act as a reservoir of lincosamide resistance genes, as exemplified by the emergence of the *lnuE* gene, previously identified in *S. suis*, in staphylococcal isolates (106). The report from Hendriksen et al. shows a certain variability of erythromycin resistance in *S. suis* among European countries during 2002 to 2004 (107). In addition, other streptococcal species were rarely found to cause diseases in swine. Within the framework of the BfT-GermVET program, Lüthje and Schwarz reported the presence of *S. dysgalactiae* subsp. *equisimilis* in diseased swine, with 21 isolates demonstrating resistance to macrolides. Among those, 13 harbored an *erm*(B) gene, one an *erm*(B) gene together with *mefA* and *msrD*, and one a *lnuB* gene (108).

In all, such an alarming prevalence of macrolide resistance in a relevant zoonotic pathogen such as *S. suis* highlights the need to prevent infections through appropriate hygienic measures.

Prevalence of Resistance to Macrolides among Streptococci from Non-Food-Producing Animals

In Brazil, six isolates of *S. dysgalactiae* subsp. *equisimilis* from horses were included in a study of antimicrobial resistance in humans, and prevalence data on resistance to macrolides were similar in isolates from the two sectors (109). In Germany, an *S. equi* subsp. *zooepidemicus* isolate with an M phenotype was recovered from a horse and harbored a *mefA* and an *msrD* gene. *S. canis* resistant to macrolides, mostly with an MLSb phenotype, has been reported from diseased dogs in Denmark and Germany (110). From dogs and cats, six *S. dysgalactiae* subsp. *equisimilis* macrolide-resistant isolates were found in Germany with five isolates harboring an *erm*(B) gene and one harboring a *mefA* and a *msrD* gene (108).

TETRACYCLINES

Tetracyclines, which were discovered in the late 1940s, are bacteriostatic antibiotics that block bacterial protein synthesis by preventing the attachment of aminoacyl-tRNA to the ribosomal acceptor A site (111). Because of their broad-spectrum activity against both Gram-positive and Gram-negative bacteria, they rapidly became one of the most widely used antibiotics (112), and consequently, the first resistant isolate was reported in 1953 in *Shigella dysenteriae* (113). Tetracycline resistance rapidly and broadly disseminated in bacteria of human, animal, and environmental origin and is now considered one of the most frequently seen resistances to antimicrobials (114). In humans, tetracyclines have largely been supplanted by beta-lactams, while they remain one of the main classes of antibiotics used in veterinary medicine (115–117). In animals, tetracyclines are also considered as growth-promoting factors when mixed with food at subtherapeutic levels, in order for food-producing animals to gain weight more quickly (111). This practice was banned in Europe at the latest on 1 January 2006 since it can promote resistance selection, as exemplified by the increase of vancomycin-resistant enterococci in animals through the use of the glycopeptide avoparcin (118). However, growth promoters are still authorized in many countries worldwide, such as in the United States, and tetracycline is again the most frequently used antibiotic class (117). The past and present excessive use of tetracyclines first of all hampers the efficacy of these molecules, but may also have unexpected side effects such as the selection of hypervirulent *S. agalactiae* clones worldwide and increasing numbers of neonate infections (119).

Tetracycline Resistance Determinants

A total of 46 *tet* or *otr* genes have been identified as tetracycline resistance determinants in 126 genera (120, 121). They are commonly divided into two main groups characterized by their mode of action: the genes coding for efflux proteins and those coding for ribosomal protection enzymes (120). In *Streptococcus* spp., *tet*(K), *tet*(L), *tet*(M), *tet*(O), *tet*(Q), and *tet*(T) are the most frequently reported genes (111, 113, 121). Tet(K) and Tet(L) code for membrane-associated efflux systems that share nearly 60% amino acid identity (111) and confer resistance to tetracycline but not to minocycline. The *tet*(K) gene was discovered on a pT181 plasmid in *Staphylococcus aureus* (122), whereas *tet*(L) was found associated with small non-conjugative plasmids in streptococci (123). In contrast, Tet(M), Tet(O), Tet(S), Tet(Q), Tet(T), and the more recently identified Tet(W)

are enzymes that protect the ribosome from the action of tetracycline, a mechanism conferring resistance to all available antibiotics of the tetracycline family. The *tet*(M) gene was concomitantly identified with *tet*(L) on streptococcal plasmids (123). It has now been extensively detected and studied in both Gram-negative and Gram-positive species and is often found on ICEs of the Tn*916*-Tn*1545* family (124–127). Since the Tn*916*-Tn*1545* elements also encode, among others, resistance to erythromycin and kanamycin, these mobile determinants promote the emergence of multiresistant isolates, as exemplified by their frequent association with the *tet*(M) and *erm*(B) resistance genes in streptococci isolates (120). The dissemination of the remaining protecting enzymes—Tet(O) (which was first discovered in *Campylobacter coli* [128]), Tet(S) (discovered in *Listeria monocytogenes* [129]), Tet(Q) (first described in *Bacteroides* species [130]), and the closely related Tet(T) (first detected in *S. pyogenes* [131])—was less efficient than the diffusion of Tet(M), probably because of the localization of the corresponding genes, which have never been reported on conjugative transposons such as Tn*916* and Tn*1545*, mentioned above. Of note, Tet(M), Tet(O), Tet(S), and Tet(Q) are closely related since they share around 78% sequence identity (113), even though they can easily be differentiated using specific primers. Tet(W) is the latest protection enzyme detected in streptococci and was first identified in *Butyrivibrio fibrisolvens* (132).

Prevalence of Tetracycline Resistance among Streptococci of Bovine or Ovine Origin

Most studies reporting tetracycline resistance in isolates of bovine or ovine origin were performed on *S. uberis*, *S. dysgalactiae*, and *S. agalactiae* in the context of clinical or subclinical mastitis. Tetracycline is often the antibiotic presenting the highest prevalence of resistance. When considering the CLSI breakpoints which categorize as tetracycline resistant all isolates presenting an MIC of >4 mg/liter, resistance rates in *S. uberis* ranged from 1.8 to 4% in Sweden between 2002 and 2009 up to 60% in Portugal in 2003 (90, 101, 133), with intermediate prevalence of 12.9 to 22% in France, 15% in England, 27.1% in the United States (1997 to 1999), and 44% in Italy (99, 134–136). In *S. dysgalactiae* prevalence is overall higher, ranging from 6% in Sweden to 76.6% in the Netherlands and 100% in Portugal and France (90, 94). Prevalence rate figures are less frequently available for *S. agalactiae* but also suggest a very high frequency of tetracycline resistance, with 33.4% in Sweden in 2002 and 37.5% in France in 2000 (133, 134).

Only a few studies have reported the molecular characterization of *tet* resistance genes (Table 3) in streptococci of bovine origin. When reported, the *tet* genes did not have a bacterial specificity and were often described in combination, such as *tet*(M)/*tet*(O), *tet*(M)/*tet*(K), or *tet*(O)/*tet*(K) (90, 94, 137, 138).

Most studies detailed here were performed in Europe in the 2000s. Having a better and updated view of the evolution of resistance in veterinary streptococci would require monitoring of tetracycline resistance in bacteria from animal origins at a larger scale.

Prevalence of Tetracycline Resistance among Streptococci of Porcine Origin

In line with *S. suis* being the major *Streptococcus* spp. in swine, numerous publications have reported antimicrobial resistance in this pathogen, mostly in diseased animals. Tetracycline, as already noted for streptococci of bovine or ovine origin, is often the antibiotic presenting the highest prevalence of resistance. The lowest rates were reported in the oldest European isolates studied (no resistance in Danish isolates collected in 1967 to 1981 and 7.7% in Swedish isolates collected in 1992 to 1997) and in the context of the ARBAO-II study performed in 2002 to 2004 (48% resistance in the Netherlands and 52.2% in Denmark in 2003) (102, 107). Higher rates were then reported in the United States (66.7% in 1986), Spain (68.0% in 2004), Poland (64.0% in 2004), Japan (86.9%), Italy (89.5%), and a pan-European study (75.1%) (107, 139–141). Several studies showed resistance rates greater than 90%, with 91.7%, 95.4% and 97.9% in China, Spain, and Brazil, respectively (142–144).

A few molecular studies detailed the *tet* genes responsible for the phenotypic resistance detected. Tet(O) is by far the most commonly detected enzyme in *S. suis*, while Tet(M) has also been reported (Table 3), either alone or in association with other Tet determinants, in particluar Tet(O). The distribution of these *tet* genes may also vary depending on the serotype, but further work on larger cohorts is needed to have statistically relevant data. The *tet*(W) gene was repeatedly reported in *S. suis*, initially in a human patient in Italy, but then also in pig isolates (140, 145, 146). Of note, the only occurrence of *tet*(B) in streptococci was reported in 17 *S. suis* isolates (17/111, 15%) in the United States (147).

Tetracycline Resistance among Other Streptococci

Tetracycline resistance in *S. canis* was reported from diseased cats and dogs, with a prevalence of 32.1% in France, 23.5% in Japan, and 27% in Portugal (including

TABLE 3 Distribution of the tetracycline resistance genes in streptococci in animal hosts

Animal host	Country	Year	Bacterial species	No. of isolates	Tetracycline genes					No. of TetR isolates[b]	Percentage of resistance (%)	Reference
					Efflux		Ribosomal protection					
					tet(K)	*tet*(L)	*tet*(M)	*tet*(O)	*tet*(S)			
Cattle	USA	1990	*S. agalactiae*	39	0	0	NT[a]	7	NT	10	25.6	137
			S. dysgalactiae	21	1	1	NT	1	NT	9	42.9	
			S. uberis	11	1		NT	1	NT	2	18.2	
Cattle	France	1984–2008	*S. agalactiae*	76	NT	NT	16	13	1	30	39.5	94
			S. dysgalactiae	32	NT	NT	5	4	4	32	100.0	
			S. uberis	101	NT	NT	23	36	3	62	61.4	
Cattle	Portugal	2002–2003	*S. agalactiae*	60	34	NT	13	20	0	34	56.7	90
			S. dysgalactiae	18	0	NT	6	6	0	18	100.0	
			S. uberis	30	0	NT	2	9	8	18	60.0	
Ovine	Italy	2004–2014	*S. uberis*	51	9	NT	12	12	NT	18	35.3	138
Pig	USA	1986	*S. suis*	21	0	0	5	NT	NT	14	66.7	103
Pig	Denmark	1989–2002	*S. suis*	103	NT	0	11	6	0	25	24.3	237
Pig	Italy	2003–2007	*S. suis*	57	0	0	2	38	0	51	89.5	140
Pig	China	2005–2012	*S. suis*	62	NT	NT	53	42	NT	57	91.9	170
				34	NT	NT	24	9	NT	28	82.4	
Pig	China	2008–2010	*S. suis*	106	NT	2	16	86	1	105	99.1	146
Dog/cat	France	2010	*S. canis*	112	NT	1	31	16	5	36	32.1	148
Dog/cat	Japan	2015	*S. canis*	68	0	0	13	10	NT	16	23.5	149
Dog/cat/horse/human[c]	Portugal	2000–2010	*S. canis*	85	NT	1	11	8	1	23	27.0	34

[a]NT, not tested.
[b]Discrepancies between the number of tetracycline-resistant isolates and the genes identified may be due to either unidentified genes or to isolates presenting an association of two or three *tet* genes.
[c]Human isolates could not be individualized.

a few isolates from horses and humans) (34, 148, 149). In these studies, tetracycline resistance was due principally to the presence of the *tet*(M) and *tet*(O) genes, alone or in combination. A study performed in Belgium on healthy individually owned cats and groups of cats noted a higher prevalence of tetracycline resistance in a cattery (52%) compared to individual animals (22.2%), most likely due to the clonal transmission of resistant strains in the cattery (150).

BETA-LACTAM RESISTANCE

Beta-lactams are the largest family of antibiotics available in both human and veterinary medicine. All members of this family act on the bacterial cell wall by covalently blocking the PBPs and thus impairing the continuous building of this protecting structure. Currently, bacterial resistance to the last generations of beta-lactams is one of the most challenging issues in both human and animal medicine. The key threats are the worldwide emergence and dissemination of inactivating enzymes such as extended-spectrum beta-lactamases, cephalosporinases (AmpCs), and carbapenemases in Gram-negative bacteria. All these resistance determinants are carried by plasmids and thus display a high capacity to efficiently disseminate in an intra- or interspecies manner. In Gram-positive bacteria, methicillin-resistant *S. aureus*—which possesses an additional PBP2A presenting a decreased affinity to beta-lactams—remains an issue in human medicine, despite the fact that its prevalence in hospitals has been considerably reduced in the past decades with improvements of hygiene measures. In veterinary medicine, methicillin-resistant *Staphylococcus pseudintermedius* is known to cause serious treatment challenges because of its associated multiresistance. However, the success of both methicillin-resistant *S. aureus* and methicillin-resistant *S. pseudintermedius* is more due to epidemic bursts of successful clones than to the mobilization of the *mecA*-carrying cassette.

Streptococci are unique among the major pathogens in the sense that they are incapable of acquiring any exogenous beta-lactam resistance genes. However, they can progressively mutate their own PBPs. Indeed, no isolate carrying a beta-lactamase (such as Gram-negative bacteria) or a new PBP (such as staphylococci) has been described yet, and a few species, including *S. pyogenes*, are even unable to develop decreased susceptibility to beta-lactams *in vitro* (151).

Beta-Lactam Resistance in Streptococci

To achieve beta-lactam resistance, streptococci sequentially modify their PBPs, specifically the class B PBP2B and PBP2X (and the class A PBP1A in the more resistant isolates). This was particularly exemplified in *S. pneumoniae*, the only *Streptococcus* spp. for which penicillin-resistance was successfully achieved and widely disseminated, where both mutated and mosaic PBPs were reported. Other less-documented genes were sporadically reported as PBP-independent penicillin-resistance mechanisms. These include the *MurMN* operon encoding enzymes that are responsible for the biosynthesis of branched muropeptide components (152), the *ciaRH* operon, a two-component signal-transducing system (153), the *adr* gene coding for a peptidoglycan *O*-acetyltransferase (154), the *stkP* gene encoding a serine/threonine kinase (155), the *pstS* gene encoding a subunit of a phosphate ABC transporter (156), and the *spr1178* gene encoding for a putative iron permease (157). Penicillin-resistant *S. pneumoniae* has widely disseminated through the success of a limited number of serotypes, selected mainly by the excessive use of antibiotics (158), but the prevalence of this resistance has considerably decreased since the early 2000s by both the reduced consumption of antibiotics and the marketing of efficient vaccines (159, 160). The presence and characterization of mutated PBPs in isolates presenting decreased susceptibilities to beta-lactam were also reported in *S. agalactiae* of human origin (69, 161, 162). Recently, a classification of *S. agalactiae* was proposed which takes into account the different mutations in the PBPs (163).

In veterinary medicine, *Streptococcus* isolates presenting full penicillin resistance have only rarely been reported, and only a few molecular studies were conducted either on laboratory strains or on field isolates presenting reduced susceptibility to beta-lactams. The presence of three groups of PBPs (PBP 1, PBP 2, and PBP 3) was demonstrated in *S. suis*, and PBP modifications were strongly suggested to be responsible for penicillin G-resistant phenotypes in both *in vitro* mutants and field isolates (164). In *S. uberis*, Haenni et al. (165) showed that both a quality control strain and field strains were capable of developing a 60-fold MIC increase after 30 cycles of exposure to penicillin G. This increase was due to the accumulation of mutations in the class B (PBP 2B and PBP 2X) and A (PBP 1A) enzymes, including the systematic presence of the two specific $E_{381}K$ and $Q_{554}E$ mutations in the PBP 2X. Interestingly, PBP analysis of seven field strains collected in Switzerland, France, and Holland and presenting MICs of 0.25 to 0.5 mg/liter also revealed the systematic presence of these two key mutations (165). However, none of the tested strains (selected either *in vitro* or by treatment on farms) could achieve full resistance, since their MICs only reached

0.25 to 2 mg/liter, which is still considered intermediately resistant.

Phenotypic Reports on Beta-Lactam Activity in Bovine Mastitis

In veterinary medicine, beta-lactam resistance has mostly been documented in bovine streptococci, namely *S. uberis*, *S. dysgalactiae*, and *S. agalactiae*. Data were gathered in cases of clinical and subclinical mastitis, a pathology for which the first-line treatment is beta-lactams. Comparison between studies can be difficult because of the heterogeneity of the methods (disc diffusion, agar diffusion, broth microdilution) and the guidelines used. If no interpretation was inferred, an isolate was considered resistant when the MIC was ≥4 mg/liter according to the CLSI breakpoints.

Most studies based on the determination of MICs report the absence of penicillin G resistance in *S. uberis* and *S. dysgalactiae*, even though isolates presenting decreased susceptibilities (0.25 to 0.5 mg/liter) were regularly reported. In France, such nonsusceptible isolates were reported in 2002, with 14.0% of the *S. uberis* showing an MIC of 0.25 mg/liter (134), and a shift toward decreased susceptibilities was suggested in 2010 based on the comparison of disk diffusion and MIC results (166). In Sweden, two studies performed successively in 2003 (133) and 2008 to 2009 (101) showed a slight shift over the years toward decreased susceptibility, with 6.0% of the *S. uberis* isolates displaying an MIC of 0.25 mg/liter and 10.0% of the *S. dysgalactiae* isolates displaying an MIC of 0.12 mg/liter in 2009, whereas only 0.9% of the *S. uberis* isolates had an MIC of 0.25 mg/liter, and all the *S. dysgalactiae* isolates were fully susceptible (MIC, <0.06 mg/liter) in 2003. In the United States, one true resistant *S. dysgalactiae* isolate (MIC, 4 mg/liter) was detected over 152 strains tested, whereas 6.8% of the *S. uberis* isolates presented MICs of 0.5 mg/liter to penicillin, and one strain displayed an MIC of 1 mg/liter (136). The VetPath data (multicenter European data) collected between 2002 and 2006 showed no true resistance, but 29.8% of isolates presented decreased susceptibility (MICs ranging from 0.25 mg/liter to 1 mg/liter) (100). Though without any MIC values, other studies also reported data on beta-lactam resistance in veterinary streptococci, often with a very low prevalence of resistance. One pan-European study performed in 2002 to 2004 showed very low levels (0 to 3.9%) of penicillin resistance (99). A Swiss study detected susceptibilities to ampicillin of 92.3% for *S. uberis* and 94.8% for *S. dysgalactiae* from cows sampled in 2011 to 2013 (167). Kalmus et al. showed 0 to 0.4% resistance to penicillin G, ampicillin, and cefalotin in Estonia between 2007 and 2009 (168). In France, 12.9% of the *S. uberis* and 1.4% of the *S. dysgalactiae* presented resistance patterns to oxacillin, but these were not confirmed by MIC determination (135). In Turkey, 94% of the *S. uberis* isolates showed susceptibility to penicillin G (169).

These different data confirm beta-lactams as efficient antibiotics against streptococci isolated from bovine mastitis. However, this slow but clear shift of strains from full toward decreased susceptibility will have to be surveyed in the future. Beta-lactam resistance development in streptococci surely does not present the same dynamic as in Gram-negative bacteria, where plasmids play a major role. However, this should not hide rampant and silent acquisition of beta-lactam resistance in streptococci of animal origin, which may one day limit the therapeutic arsenal available for veterinarians.

Beta-Lactam Resistance Outside the Context of Cattle Mastitis

Antibiotic resistance was also monitored in *S. suis* isolated from pigs, and several studies reported the absence of resistance to any beta-lactams. Nevertheless, isolates presenting particularly high MICs to penicillin G were also recurrently reported, with unfortunately, no concomitant molecular work on the underlying mechanisms of resistance. Indeed, 4% of the Spanish isolates displayed MICs ranging from 4 to 16 mg/liter, whereas two Chinese studies reported 2.1% and 9.5% of isolates with an MIC of ≥4 mg/liter (142, 143, 170). In the Netherlands, 0.5% and 0.3% of over 1,163 isolates of *S. suis* tested were considered resistant to penicillin G and ampicillin between 2013 and 2015 (171). In Japan, Poland, and Portugal, resistance was reported in 0.9%, 8.1%, and 13.0% of the isolates, respectively (107, 141). However, despite these cases, beta-lactams can still be recommended as first-line antibiotics for the treatment of *S. suis*.

Aside from *S. suis* and streptococci isolated from bovine mastitis, reports of veterinary streptococci are quite rare. Beta-lactam resistance was described once in *S. dysgalactiae* subspecies *equisimilis* isolated from swine in Brazil and in four studies of *S. canis* isolated from pets and horses in France, Japan, Belgium, and Portugal (34, 148–150, 172), and these five studies found full susceptibility of all isolates to penicillin G.

FLUOROQUINOLONE RESISTANCE

Quinolones are not active against streptococci, because of their intrinsic resistance. However, fluoroquinolones

may be an alternative to beta-lactam antibiotics to treat streptococcal infections. The main agents used in veterinary medicine are enrofloxacin, marbofloxacin, danofloxacin, and the more recent pradofloxacin.

Resistance to fluoroquinolones is generally mediated by point mutations in the quinolone resistance-determinants regions of the *gyrA* and *parC* genes (173). Furthermore, plasmidic *qnr* genes participate in the dissemination of low-level resistance, but they have never been reported in streptococci. Efflux pumps also play a role in fluoroquinolone resistance, as has been proved for the SatAB, an ABC transporter, in *S. suis* (174).

Fluoroquinolone-Resistance Phenotypes

Resistance to fluoroquinolones has rarely been reported in veterinary streptococci. Moreover, in the fluoroquinolone family, there is a wide variability of the agents tested (enrofloxacin and ciprofloxacin are the most frequently used), thus making comparisons among studies difficult.

A 1.5% prevalence of resistance to enrofloxacin in *S. uberis* and 5.5% in *S. dysgalactiae* was reported in France in 2010 (135). In the same bacterial species, MICs ranging from 0.5 to 2 mg/liter were observed in Sweden (101). These apparently elevated MICs are constitutive of streptococci, which have a basal MIC higher than that of *Enterobacteriaceae* or staphylococci. In a study performed between 1994 and 2001, the same range of MICs was reported, and no increase in the resistance rate was observed over the years (175). Except for three resistant strains (MIC, 4 mg/liter), all *S. uberis* and *S. dysgalactiae* isolates collected in a multicenter European study presented MICs to marbofloxacin ranging from 0.25 to 2 mg/liter (176). In *S. suis*, the resistance rates to enrofloxacin determined in a pan-European study performed in 2009 to 2012 and to ciprofloxacin determined in Japan in 1987 to 1996 were very similar: 0.7% and 0.3%, respectively (177). Enrofloxacin resistance was also observed in *S. canis* in France, where MICs ranged from 0.25 to 2 mg/liter (148). *Streptococcus* spp. isolated from cats and dogs were studied through the ComPath European network: no resistance was reported in dermatological samples, whereas 1.8% of the cats and 4.0% of the dogs presenting with a respiratory tract infection carried enrofloxacin-resistant streptococci (178, 179).

ROLE OF THE ICES IN THE EVOLUTION OF RESISTANCE

MGEs play a major role in the dissemination of antibiotic resistance genes. MGEs mostly comprise conjugative plasmids, transposons, phages, and ICEs (initially named conjugative transposons). ICEs are chromosomal, self-transmissible MGEs that are capable of promoting their excision, conjugation, and site-specific integration in a recipient cell (180, 181). One of the most emblematic members of the ICEs is the Tn*916*-Tn*1545* family, which carries *tet*(M) and other antibiotic resistance genes (126, 127, 182, 183).

ICEs have been widely reported in streptococci, and they were recently detected in all *Streptococcus* spp. for which at least one complete genome was available, with *S. suis* being the most "colonized" species (184, 185). In human clinical streptococcal isolates, *erm* and *tet* resistance genes were recurrently reported on ICEs, such as *erm*(B) on ICE*Sp1116* and *erm*(TR)-*tet*(O) on ICE*Sp2905* in *S. pyogenes* (186, 187), *erm*(TR) on ICE*Sag*TR7 in *S. agalactiae* (188), and *erm*(B) and *tet*(O) on ICE*SsD9* in *S. suis* (189). Interestingly, resistance genes can also be mobilized by coresident ICEs, as demonstrated by the mobilization of an *erm*(T)-carrying plasmid in *S. dysgalactiae* subsp. *equisimilis* (190). Other antibiotic resistance determinants can also be found on ICEs, as exemplified by the presence of *tet*(M) and a chloramphenicol acetyl-transferase on ICE*Sp*23FST81 from *S. agalactiae* (191), lincosamide resistance (*lsa* genes) on different ICEs in *S. agalactiae* (192), and a multidrug resistance cluster on ICE*Ssu*NC28 carried by *S. suis* (193). Moreover, ICEs originating from different streptococcal species may form hybrids that can further transfer *in vitro* to a third streptococcal species (194). This illustrates the wide distribution and the plasticity of these MGEs and thus their role in the dissemination of resistance genes. Finally, resistance determinants may be adjacent to—and not inside—an ICE. This is exemplified by the first vancomycin-resistance determinants in streptococci, the *vanG* operons, which were identified in one *S. agalactiae* and two *S. anginosus* isolates (195). These *vanG* operons were immediately followed by a large chromosomal element named ICE-r (ICE-like sequences). A plausible hypothesis is that the integration of ICE-r in the streptococcal chromosome may have favored the subsequent integration of the *vanG* element.

Except for elements from the Tn*916*-Tn*1545* family which were broadly reported in different streptococcal species originating from diverse animal hosts (9, 94, 170, 196), ICEs carrying resistance genes have rarely been reported in streptococci from animal origin. Indeed, only the mosaic *tet*(O/W/32/O) carried on ICE*Ssu32457* in *S. suis*, which could then be transferred to *S. pneumoniae*, *S. pyogenes*, and *S. agalactiae* (197), as well as the lincomycin-resistance gene *lsa* (192) were described on

such MGEs. This will likely change in the near future, since new research perspectives are emerging with the democratized access to high-throughput sequencing technologies and the subsequent databases (185, 198).

CONCLUSION

In veterinary medicine streptococci are frequent pathogens not only in food-producing but also in companion animals. However, as far as public health is concerned, there are few situations in which streptococci of animal origin may cause risk for humans, and vice-versa. Among those, *S. suis* and, to a lesser extent, *S. agalactiae* are likely the most relevant examples, and are both considered zoonotic pathogens. Studies of resistance to antimicrobials in streptococci of animal origin have largely focused on tetracyclines and macrolides/lincosamides, which are widely used in the animal sector globally. Accordingly, high resistance rates to these molecules have frequently been observed, which is also in line with specific niches covering major animal diseases, such as cattle mastitis of streptococcal origin. Molecular investigations highlighted the diversity of the resistance genes of the *tet* and *erm* families, together with the pivotal role of the ICEs. Nonetheless, most data originate from Europe, and there is a need for larger prevalence and molecular studies on a global scale. Of note, despite the wide use of penicillins to treat streptococcal infections, resistance to beta-lactams does not appear to be a crucial issue in veterinary streptococci, in contrast to what has been observed with the human-specific *S. pneumoniae*. In all, as in humans, antimicrobial resistance in *Streptococcus* of animal origin may largely differ depending on the *Streptococcus* sp. and therefore should not be considered as a whole.

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