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Short communication: Streptococcus species isolated from mastitis milk samples in Germany and their resistance to antimicrobial agents

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ABSTRACT

Mastitis is one of the most frequent infectious diseases in dairy cattle and is a reason for antimicrobial drug usage in dairy cows. The bacteria involved in bovine mastitis are mainly *Streptococcus* spp., *Staphylococcus* spp., and coliforms. The aim of this study was to determine antimicrobial resistance among *Streptococcus* spp. isolated from bovine mastitis milk. Antimicrobial resistance in *Strep. uberis* (n = 227), *Strep. dysgalactiae* (n = 49), and *Strep. agalactiae* (n = 3) was determined for 9 antimicrobial agents using the broth microdilution method in accordance with Clinical and Laboratory Standards Institute recommendations. Of all *Streptococcus* spp., 13% were multidrug resistant. The rate of multidrug resistance was higher among *Strep. uberis* (15%) than among *Strep. dysgalactiae* (6%) and *Strep. agalactiae* (0%). Resistance to tetracycline was the most common, followed by resistance to erythromycin, pirlimycin, and gentamicin. Resistance rates were higher on farms with more than 80 cows compared with those with fewer than 20 cows. β-Lactams should remain the drugs of choice in the treatment of streptococcal mastitis. The slightly elevated minimum inhibitory concentrations determined for these antibiotics may indicate, however, the emergence of resistant streptococci. To identify such changes in susceptibility as early as possible, antimicrobial resistance in streptococci should be surveyed regularly.
Key words: antibiotic, microdilution, drug

Short Communication

Mastitis is one of the most frequent infectious diseases in dairy cattle and is a reason for antimicrobial drug usage in dairy cows (Pol and Ruegg, 2007b). Bacteria involved in bovine mastitis are classified as either contagious or environmental pathogens based on their epidemiological association with the disease (Bramley, 1985; Sandholm et al., 1990). Streptococcal species are major mastitis pathogens, along with *Staphylococcus aureus* and coliforms. *Streptococcus agalactiae* is cow-associated and well adapted to the mammary gland, whereas *Streptococcus dysgalactiae* and *Streptococcus uberis* are environmental pathogens; *Strep. uberis* is one of the most common pathogens isolated from clinical mastitis (Guérin-Faublée et al., 2002; Botrel et al., 2010).

Mastitis therapy is commonly initiated before susceptibility testing of the pathogen (Guterbock et al., 1993; Guérin-Faublée et al., 2002; Hendriksen et al., 2008). The most commonly used antimicrobial classes for the treatment of streptococcal mastitis are β-lactams and macrolides (Denamiel et al., 2005; Tenhagen et al., 2006; Haenni et al., 2010; Kalmus et al., 2011). Because the emergence of resistant pathogens is of growing concern in veterinary medicine, performing susceptibility tests during the bacteriological examination of mastitis milk samples is an important basis for the selection of the appropriate chemotherapeutic agents (Schwarz et al., 2003). The method of choice for susceptibility testing is considered the dilution test, in accordance with the Clinical and Laboratory Standards Institute (**CLSI**) (Schwarz et al., 2003; Luhofer et al., 2004).

Antimicrobial resistance is an area of concern in both human and veterinary medicine, underlining the importance of surveillance of antimicrobial resistance to acquire information about the extent of said resistance and to observe the effects of interventions (Schwarz et al., 2001). Although several studies have been conducted on the antimicrobial resistance of streptococci (Guérin-Faublée et al., 2002; Rossitto et al., 2002; Denamiel et al., 2005; Schröder et al., 2005; Kaspar, 2006; Pitkälä et al., 2008; Bengtsson et al., 2009; Nam et al., 2009), only limited data are available on multidrug resistance (Guérin-Faublée et al., 2002) and vancomycin resistance (Krabisch et al., 1999) of streptococci from dairy cows. The aim of this study was therefore to determine the resistance patterns of recently isolated

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Streptococcus spp. from bovine mastitis milk samples in Germany.

In total, 279 streptococci isolates from mastitis milk samples were used in this study. All isolates were obtained from routine submissions of bovine milk to the Aulendorf state veterinary diagnostic center (Aulendorf, Germany). Approximately 10,000 quarter milk samples were collected and analyzed routinely from 5 geographic locations in southwestern Germany between July and December 2009. Only *Streptococcus* spp. isolated from milk samples of mastitis cases showing abnormal changes, such as pus or flakes, or samples of milk with SCC >250,000 cells/mL were used in the study. Cows known to have been treated with antimicrobials in the last 4 wk before sampling were excluded from the study. To avoid duplicate samples, the isolates were limited to one per farm. Milk samples were classified as positive if at least 5 cfu were isolated. Samples were excluded from the study if they were classified as contaminated (more than 2 different bacterial species).

Milk samples (10 μL) were streaked onto 5% sheep blood agar (Oxoid, Wesel, Germany) and incubated at 37°C for 18 to 24 h. Isolates were identified using conventional methods such as colony morphology, esculin reaction, catalase test, and Gram staining. Additionally, all isolates were biochemically identified using the API 20 Strep system (bioMérieux, Nürtingen, Germany). The isolates were stored in cryovials (Mast Diagnostika, Reinfeld, Germany) at −80°C. All streptococci were checked for viability by streaking on sheep blood agar and incubating at 37°C for 24 h before antimicrobial resistance testing.

Minimum inhibitory concentrations were determined using the broth microdilution method in accordance with the recommendations of CLSI (2008). The selected panel consisted of a specially designed microtiter plate (Merlin, Bornheim-Hersel, Germany) with 9 antimicrobials against gram-positive cocci approved for therapeutic use in dairy cows in Germany. In addition, vancomycin (which is only approved for use in human medicine) was included in the study because of increasing resistance to this compound. The widest possible range of antimicrobial concentrations, with a minimum of one 2-fold dilution higher and four 2-fold dilutions lower than the respective breakpoints, was selected. The range of the concentration of the antimicrobials tested is shown in Table 1. For testing, 3 to 5 colonies were transferred into 5 mL of cation-adjusted Mueller-Hinton broth (**CAMHB**, Oxoid) and incubated for 16 to 20 h at 35°C. Next, approximately 0.5 mL of this pre-inoculum was transferred to 5 mL of CAMHB and adjusted to a turbidity of McFarland standard 0.5 to obtain an inoculum with approximately 1.5×10^8 cfu/mL. Subsequently, following the recommendations of the manufacturer, 200 μL was transferred from the inoculum to 11 mL of CAMHB. Each well was filled with 100 μL of the adjusted inoculum and sealed with transparent covering tape. To verify the inoculum density of each isolate, 10 μL of the final inoculum was diluted in 10 mL of 0.9% NaCl, and 100 μL of this dilution was plated onto blood agar plates. The microtiter plates were incubated aerobically for 16 to 20 h at 35°C and then scored by visual examination. The MIC was defined as the lowest antimicrobial concentration that inhibited bacterial growth. The breakpoints used were those recommended by the CLSI (2008) for streptococci. Multidrug resistance was defined as resistance to 3 or more classes of antimicrobial agents (Schwarz et al., 2010). The control strains used were *Enterococcus faecalis* ATCC 29212 and *Staphylococcus aureus* ATCC 29213.

The χ^2-test according to McNemar (Curiale et al., 1997) was used to assess the variables obtained. The level of significance for all comparisons was $\alpha = 0.05$. Overall, approximately 10,000 quarter milk samples were analyzed in the routine laboratory during the examination period. Of these, 279 *Streptococcus* spp. (227 *Strep. uberis*, 49 *Strep. dysgalactiae*, and 3 *Strep. agalactiae*) were selected for the study (Table 2).

As expected, isolates of *Strep. uberis* were more often resistant than isolates of *Strep. dysgalactiae* or *Strep. agalactiae* (Guérin-Faublée et al., 2002). Of all *Streptococcus* spp. tested, 13% were multidrug resistant and 43% were resistant to at least one antimicrobial agent. The multidrug resistance rate was higher ($P < 0.05$) among *Strep. uberis* isolates than among *Strep. dysgalactiae* and *Strep. agalactiae* isolates and was higher than previously reported (Guérin-Faublée et al., 2002).

Resistance to tetracycline and erythromycin was detected most frequently, in accordance with previous findings in Germany and other countries across the world (Guérin-Faublée et al., 2002; Denamiel et al., 2005; Schröder et al., 2005; Kaspar, 2006; GERMAP, 2008; Hendriksen et al., 2008; Pitkälä et al., 2008; Nam et al., 2009). In contrast, a recent survey from Estonia reported lower rates of erythromycin resistance among streptococci (Kalmus et al., 2011).

Pirlimycin resistance among streptococci has been reported previously (Rossitto et al., 2002; Pol and Ruegg, 2007a; Schmitt-Van de Leemput and Zadoks, 2007; GERMAP, 2008; Haenni et al., 2010). In the present study, high levels of pirlimycin resistance (MIC ≥16 mg/L) were found (Table 1), whereby *Strep. uberis* isolates showed greater ($P < 0.05$) resistance to this drug than did the other streptococci. Pirlimycin, a lincosamide used to treat mastitis caused by gram-positive cocci in dairy cows, is approved only for veterinary use and is available only for intramammary administration.

Table 1. Minimum inhibitory concentrations determined for 279 *Streptococcus* species isolates[1]

	No. of strains at MIC (μg/mL)													
Antimicrobial/species	0.015	0.031	0.062	0.125	0.25	0.5	1	2	4	8	16	32	64	>64
Ampicillin														
Strep. uberis		96	45	73	10	3								
Strep. dysgalactiae		46	2	1										
Strep. agalactiae		3												
Penicillin														
Strep. uberis	95	19	56	52	5									
Strep. dysgalactiae	45	1	1	2										
Strep. agalactiae	2	1												
Amoxicillin/clavulanic acid														
Strep. uberis		98	25	88	16									
Strep. dysgalactiae		46	2	1										
Strep. agalactiae		3												
Cefazolin														
Strep. uberis			12	86	35	86	7	1						
Strep. dysgalactiae			9	37		2	1							
Strep. agalactiae				3										
Gentamicin														
Strep. uberis						2	16	53	85	66	1	4		
Strep. dysgalactiae						19	25	3	2					
Strep. agalactiae									3					
Erythromycin														
Strep. uberis		13	47	78	30	7	1	19					3	29
Strep. dysgalactiae		3	10	23	6		1	1					1	4
Strep. agalactiae				3										
Tetracycline														
Strep. uberis				26	68	22	7	7	1	1	23	31	39	2
Strep. dysgalactiae				1		8	17	8	2		9	3	1	0
Strep. agalactiae						1					1	1		
Pirlimycin														
Strep. uberis				116	26	11	7	24	13	7	3	20		
Strep. dysgalactiae				36	5		1	1	2	1		13		
Strep. agalactiae				1	1	1								
Vancomycin														
Strep. uberis				1	158	68								
Strep. dysgalactiae				3	40	6								
Strep. agalactiae						3								

[1] Shaded areas indicate the concentration ranges of the antimicrobials tested. The breakpoints used are indicated by vertical lines (CLSI, 2008).

Table 2. Antimicrobial resistance pattern of 279 *Streptococcus* spp. isolates from mastitis milk samples in Germany

Resistance to *x* classes of antimicrobials	*Strep. uberis* (n = 227)	*Strep. dysgalactiae* (n = 49)	*Strep. agalactiae* (n = 3)	Total (%) (n = 279)
4	2	0	0	2 (1)
3	32	3	0	35 (13)
2	21	6	0	27 (10)
1	50	7	0	57 (20)

Pol and Ruegg (2007a) demonstrated that for *Streptococcus* spp., the MIC of pirlimycin increased in relation to the increase of exposure to pirlimycin. The increase in pirlimycin resistance emphasizes the importance of surveillance studies to determine whether this trend will continue.

Combined resistance to macrolides and lincosamides was found in 38 isolates. Resistance to macrolides and lincosamides is widespread among streptococci and the possibility exists of horizontal transfer of resistance genes (Loch et al., 2005; Martel et al., 2005; Schmitt-Van de Leemput and Zadoks, 2007). Because of the wide distribution of the *erm* (erythromycin ribosome methylase) gene and the possible development of complete cross-resistance, erythromycin-resistant gram-positive cocci should not be treated with 16-limbed macrolides (macrolides with a 16-membered lactone circle; Werckenthin et al., 2005).

A low level of gentamicin resistance was observed; however, almost one-third of the streptococci showed elevated MIC. The results for gentamicin are difficult to compare to the literature, because different methods and breakpoints have been used in previous studies. For example, Schröder et al. (2005) and Nam et al. (2009) reported that up to 93% of streptococci were resistant to gentamicin as tested by disk diffusion. Nevertheless, our results are comparable to and lower than the 10% of *Strep. uberis* that were resistant to gentamicin in a report from Germany by Kaspar (2006).

In contrast to the relatively high rate of penicillin resistance (approximately 10%) reported in Asia (Ajariyakhajorn and Samngamnim, 2003; Nam et al., 2009), none of the streptococci in the present study was resistant to penicillin. Resistance to penicillin has not been observed in streptococci in Germany, France, Sweden, or Finland (Guérin-Faublée et al., 2002; Schröder et al., 2005; Pitkälä et al., 2008; Bengtsson et al., 2009). Decreased susceptibility to penicillin has, however, been reported previously (Erskine et al., 2002; Guérin-Faublée et al., 2002; Rossitto et al., 2002). Haenni et al. (2010) reported that a subpopulation of *Strep. uberis* field isolates shifted toward resistance against penicillin, despite the fact that all of these isolates were still considered sensitive to this antimicrobial.

Because southern Germany has many small dairy farms, we classified the farms into 3 categories according to their size: farms with <20 cows (n = 33), farms with 20 to 80 cows (n = 208), and farms with >80 cows (n = 31). Based on these classifications, it was interesting to note that the larger the farm, the greater the number of resistant streptococci obtained: 30, 43, and 58%, respectively, for farms with <20 cows, farms with 20 to 80 cows, and farms with >80 cows. Resistance rates were higher ($P < 0.05$) in the larger farms compared with the smaller (<20 cows) farms. This could be related to a greater usage of antimicrobials in the larger farms or to faster spread of resistance genes in a polymicrobial surrounding (Schwarz and Noble, 1999; Schwarz and Chaslus-Dancla, 2001). Further studies are needed to gather information concerning the extent of infectious diseases, usage of antimicrobial agents, farm management, and so on, to determine if the use of antimicrobials is correlated with the occurrence of resistant bacteria.

In the present study, milk samples from 20 administrative districts in southwestern Germany were studied. Because the samples were sent to the laboratory for routine purposes, the number of isolates obtained from each district varied. It was interesting to observe that resistance rates were highest in the districts in which a high number of isolates was obtained. These districts have cattle regions with the greatest density of cattle from most dairy farms within the catchment area of the laboratory. Such high resistance rates could be related to local factors such as the increased usage of antimicrobials and, therefore, increased selection of resistant bacteria that would render clinically resistant streptococci.

Resistant *Streptococcus* spp. were detected consistently from July to December; higher rates were noted from August to November with a peak in October (Figure 1). Seasonality of resistance has been described for *Strep. pneumoniae* in humans, and also for *Escherichia coli* O157:H7 recovered from feedlots (Marco et al., 2000; Aslam et al., 2010). Olde Riekerink et al. (2007) described the seasonal distribution of streptococcal species. They found that the highest incidence rate of clinical mastitis was caused by *Strep. uberis* in August.

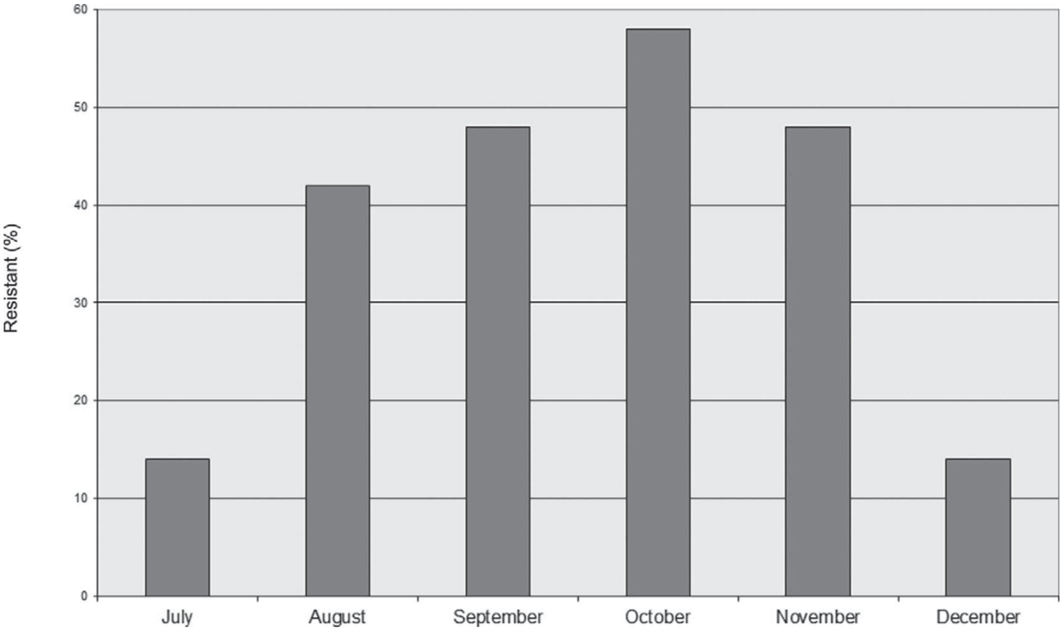

Figure 1. Monthly resistance rates of 279 *Streptococcus* species isolates from 20 districts in southwestern Germany.

In combination with the seasonality of antimicrobial resistance found in the present study, this may explain our observation that the highest resistance rate was noted in October.

In conclusion, the results of the present study showed that resistance to tetracycline was the most common, followed by resistance to erythromycin, pirlimycin, and gentamicin. The resistance rates of *Strep. uberis* were much higher than those of *Strep. dysgalactiae* and *Strep. agalactiae*. A relatively high number of streptococci were multidrug resistant. Resistance rates were higher on farms with more than 80 cows compared with those with fewer than 20 cows. The presence of vancomycin-resistant streptococci in Germany, as reported previously (Krabisch et al., 1999), could not be confirmed in the present study. The absence of resistance to penicillin and ampicillin observed in this study indicates that β-lactam antibiotics should remain the drugs of choice in the treatment of streptococcal mastitis. However, the slightly elevated MIC determined for these antimicrobials may indicate the emergence of resistant streptococci. Consequently, to make the right decisions for bovine mastitis therapy, continuous surveillance of antimicrobial-resistant mastitis pathogens is necessary.

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