In-vitro antimicrobial resistance of *Pasteurella multocida* and *Mannheimia haemolytica* from bovine mastitis on Bavarian dairy farms between 2015 and 2023

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Abstract

As the leading disease in dairy cows, mastitis and its major pathogens have been extensively researched. However, mastitis can also be caused by other, opportunistic pathogens, such as *Pasteurella (P.) multocida* and *Mannheimia (M.) haemolytica*, which are usually associated with bovine respiratory disease. To better understand the effects of these mastitis pathogens, the objective of this study was to describe the *in-vitro* antimicrobial resistance of *P. multocida* and *M. haemolytica* in quarter milk samples from Bavarian dairy farms between 2015 and 2023. *P. multocida* was isolated almost as frequently from clinical (48.6%), as from subclinical cases (51.1%), while samples with *M. haemolytica* came predominantly from clinical mastitis (82%). And while *P. multocida* was isolated in roughly equal parts (49.6% vs. 50.4%) from samples of herd screenings as well as individual submissions, *M. haemolytica* was more frequently found in individually submitted samples (87.2%). *P. multocida* was *in-vitro* mostly resistant against erythromycin (81.4%) and pirlimycin (95%), and *M. haemolytica* against erythromycin (89.7%), pirlimycin (87.2%), and oxacillin (58.9%). Yet they showed only few resistances to the other tested antimicrobials. The high occurrence of resistances against those few antimicrobials were also reflected in a high percentage of multiple resistances (83.7%). As antimicrobial resistances of those pathogens vary throughout different regions, the numbers in this study were mostly consistent with those from other studies from Germany or Austria. In general, low resistances to penicillin were reported when *P. multocida* and *M. haemolytica* were isolated from cases of mastitis, as well as a high success rate in eliminating the pathogens from the udder. However, the possibility of self-cure remains unexplored for these pathogens. When treatment with antimicrobials was selected, penicillin seemed to be the antimicrobial of choice for mastitis caused by *P. multocida* and *M. haemolytica*.

Keywords: bovine mastitis, Gram-negative mastitis pathogens, minor pathogens, antimicrobial resistance

Introduction

Mastitis is one of the leading diseases of dairy cows worldwide [1]. It has many causative agents, the most common being bacteria [2]. Best known for causing bovine mastitis are pathogens such as *Staphylococcus (St.) aureus, Streptococcus (S.) dysgalactiae, Streptococcus (S.) agalactiae, Streptococcus (S.) uberis*, and *Escherichia (E.) coli* [3]. But there are a many more pathogens that can cause mastitis. While some are acclimated to the udder, also known as contagious mastitis pathogens, others are environmental pathogens and can cause opportunistic infections [4, 5]. Those environmental pathogens can cause varying other diseases and can be found on different areas of the body. An example for this are *Pasteurella (P.) multocida* and *Mannheimia (M.) haemolytica*.

P. multocida and *M. haemolytica* are Gram-negative bacteria that are not primarily known as mastitis pathogens. Both are usually associated with bovine respiratory disease (BRD), a disease which can occur when factors such as stress weaken the immune system [6]. *P. multocida* are most known as bovine nasopharyngeal commensals and opportunistic pathogens [7], while *M. haemolytica* is considered the most important pathogen of the BRD complex, in part because of its virulence factors causing high morbidity [8].

Cases of the two pathogens causing mastitis are rare. *P. multocida* mastitis has been reported mostly in case-studies [7, 9], meanwhile, *M. haemolytica* is more known to cause mastitis in sheep [10]. Although the source of the infection often remains unknown, the upper respiratory system of calves and lambs has been discussed as an important reservoir for both pathogens, the transmission taking place during suckling [9, 10] and anecdotal reports describe rises in intramammary infections with *Pasteurella* or *Mannheimia* spp. in herds with nurse-cows. Unfortunately, due to the rarity of the infections, data on the antimicrobial resistance (AMR) profiles of *P. multocida* and *M. haemolytica* isolated from bovine mastitis are hard to find. Most of the time, the cases were treated according to the results of susceptibility testing of the isolated pathogen with antibiotics (e.g., Penicillin for *P. multocida*) [7]. Conclusive data of AMR profiles are mostly of isolates

from BRD [11].
The objective of this retrospective study was to assess the *in-vitro* AMR of *P. multocida* and *M. haemolytica* isolated from bovine mastitis in Bavaria, Germany, from 2015 to 2023.

Material and Methods

Sample Population: All quarter milk samples with either *P. multocida* or *M. haemolytica* isolates that were submitted to the laboratory of the Bavarian Animal Health Services e. V. (TGD) between 2015 and 2023 were included in the analysis. The samples were collected either by TGD technicians during herd screenings or by veterinarians and farmers from individual cows. Herd screenings were carried out for example to improve udder health, and pre-dry-off for selective dry-cow therapy. Herds with fewer than 60 cows were usually examined in full, while in larger herds sample sizes were chosen based on the number of lactating cows and the reason for sampling.
Visually abnormal milk, i.e. clinical mastitis, and the score of a California Mastitis Test (CMT) were recorded by either on-farm personnel at the time of sampling or by TGD staff upon arrival of the samples in the laboratory. The milk was aseptically collected in 9 ml sample tubes with boric acid and shipped cooled (herd tests) or uncooled to the laboratory.
Laboratory Analysis: In the TGD laboratory the samples were processed in accordance with the German Veterinary Association´s (DVG) Guidelines ([12], or respective edition). Since this as a retrospective study IACUC approval was not necessary. Upon arrival in the laboratory, the quarter milk samples were inoculated onto one quarter of an Aesculin-blood-agar plate. The inoculation loops used were calibrated according to DVG Guidelines. The plates were then incubated at 36 +/- 1°C for 18-24 hours and monitored for cultural growth. Colonies formed were evaluated by colony forming units (cfu) and morphology. For non-coliform Gram-negative isolates, cultures with two or more cfu and a positive CMT, or isolates that grew in pure culture, were classified as pathogenic. Gram-negative rods with colony morphology fitting *P. multocida* or *M. haemolytica*, were differentiated with classic biochemical differentiation methods (2015) and MALDI-TOF-MS (Bruker Corporation) (after 2015) to determine the bacterial species.
The pathogens´ AMR were assessed by breakpoint analysis using a broth microdilution (breakpoint method, Micronaut-S-System, Merlin Diagnostica GmBH). For the analysis microtiter plates Micronaut-S Mastitis 3 (Penicillin, ampicillin, oxacillin, amoxicillin/clavulanate, kanamycin/cefalexin, cefazolin, cefoperazone, cefquinome, marbofloxacin, pirlimycin, and erythromycin) or Micronaut-S Mastitis 4 (Ampicillin, cefoperazone, amoxicillin/clavulanate, kanamycin/cefalexin, oxacillin, erythromycin, marbofloxacin, and pirlimycin) were used. Each microtiter plate also contained predestined wells for growth control. The program used for MIC interpretation was MCN 6 (version MCN 6.00 – 08.01.2018 Rel. 89 or preceding versions; Demo Computer GmBH and Merlin Diagnostica GmBH).
Breakpoints were evaluated with a photometer (Tecan Sunrise, Demo Computer GmBH) and the program MCN6 version 6.00 and visual post-control and chosen in accordance with CLSI-documents [13], where available. Breakpoints that were not available for the specific bacteria and indication of mastitis in dairy cattle were taken from values for human medicine, similar pathogens, or different indications in the DVG guidelines. Intermediate results were included as resistant. Multidrug resistance (MDR) was defined as isolates that were resistant to more than one antimicrobial.
Statistical analysis: The statistical analysis was done in SAS 9.4 (SAS Analytics Software Institute Inc., SAS Institute GmbH Heidelberg). To summarize breakpoint observations, PROC FREQ procedures were used by year for each pathogen and mastitis status. Differences in MIC distributions and the odds ratio of each pathogen-antimicrobial-combination were compared by year (CHI SQUARE). Only unadjusted p-values of the PROC FREQ procedures were reported. Cochran Armitage was used for trend analysis across all years (PROC FREQ). All figures were created in Excel (Microsoft Excel for Microsoft 365 MSO, Version 2302). Missing data were ignored and α was set at 0.05.

Results

Sample Population Description: In total, 3,503,410 quarter milk samples from 757,562 cows and 17,929 herds were analyzed in the TGD laboratory between 2015 and 2023. Of those, 319 samples from 223 herds contained either *P. multocida* or *M. haemolytica* and were analyzed with breakpoint analysis during the 9-year-period (Table 1). All isolates of *M. haemolytica* came from a single cow per farm. In contrast, 95% (n=229) of *P. multocida* were isolated from one cow per herd. However, in 3.7% (n=9) there were two positive cows per herd and one herd had 3 cows with *P. multocida* isolates at the same sampling date. In short, the vast majority of isolates (94.4%, n=294) was only one isolate per cow, herd, and sampling.
Of the two pathogens, *P. multocida* was isolated more frequently (n=280), with a slight increase in the number of positive samples over the 9 years (p=0.05). *M. haemolytica* (n=39) had only a few isolates each year and no temporal change in the number of isolates was observed (p=0.88, table 1).

Table 1: Distribution of isolates of *Pasteurella multocida* and *Mannheimia haemolytica* from quarter milk samples by health status and year analyzed with broth microdilution between 2015 and 2023.

Pathogen	Year	All isolates (N)	Clinical status of quarter		
			Healthy[1] (%)	Subclinical mastitis (%)	Clinical mastitis (%)
Pasteurella multocida	**all**	**280**	**0.3**	**51.1**	**48.6**
	2015	21	-	52	48
	2016	18	-	50	50
	2017	27	-	44	56
	2018	31	-	74	26
	2019	36	3	39	58
	2020	40	-	40	60
	2021	37	-	49	51
	2022	38	-	50	50
	2023	32	-	66	34
Mannheimia haemolytica	**all**	**39**	**2.6**	**15.4**	**82.0**
	2015	3	-	-	100
	2016	5	-	20	80
	2017	4	3	25	75
	2018	2	50	-	50
	2019	4	-	25	75
	2020	7	-	29	71
	2021	4	-	-	100
	2022	5	-	-	100
	2023	5	-	20	80

[1] Negative California Mastitis Test results

Only three *P. multocida* isolates originated from healthy quarters, while nearly as many positive samples were from clinical mastitis cases (51.1%), as subclinical mastitis cases (48.6%). This did not change over

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Table 2: Distribution of MIC, MIC50 and MIC90 for *Pasteurella multocida* of quarter milk samples by antimicrobial, vertical lines indicate breakpoints. The MIC50 and MIC90 (M50/90) denote the MIC where 50% or 90% of isolates were susceptible to tested antibiotics, respectively.

Antimicrobial	MIC (µg/mL)				
Penicillin	**<=0.125**	**0.25**	**>=0.5**		
	97.3% M50/90	2.0%	0.7%		
Ampicillin		**<=4**	**>16**		
		99.3% M50/90	0.7%		
Amoxicillin/ Clavulanate	**<=4/2**	**8/4**	**16/8**	**>=32/16**	
	93.6% M50/90	4.6%	1.1%	0.7%	
Oxacillin	**<=1**	**2**	**>=4**		
	88.6% M50	5.4% M90	6.1%		
Kanamycin/ Cefalexin	**<=4/0.4**	**8/0.8**	**16/1.6**	**>=32/3.2**	
	80.9% M50	10.8% M90	7.2%	1.1%	
Cefazolin	**<=4**	**8**	**16**	**>=32**	
	97.8% M50/90	0.4%	0.4%	1.4%	
Cefoperazone	**<=2**	**4**	**8**	**>=16**	
	98.0% M50/90	0.8%	0.4%	0.8%	
Cefquinome	**<=1**	**2**	**4**	**>=8**	
	96.8% M50/90	2.4%	0.4%	0.4%	
Marbofloxacin	**<=0.25**	**0.5**	**1**	**>=2**	
	91.4% M50/90	3.6%	4.6%	0.4%	
Erythromycin	**<=0.25**	**0.5**	**1**	**2**	**>=4**
	10.4%	8.2%	20.7%	39.6% M50	21.1% M90
Pirlimycin	**<=1**	**2**	**>=4**		
	4.6%	0.4%	95.0% M50/90		

time (p=0.2). In contrast, over the years (p=0.12) the majority of *M. haemolytica* isolates originated mainly from clinical mastitis cases (82%), while isolates from subclinical (15.4%) or healthy quarters (2.6%) were few (Table 1).

When looking at submitted samples that contained *P. multocida*, the quarter milk samples were fairly evenly distributed between individual submissions by farmers (49.6%) and herd screenings (50.4%), with no change over the years (p=0.58). *P. multocida* from individual submissions were isolated slightly more often from subclinical and less frequently from clinical cases, than those from herd screenings (p=0.03, results not shown).

M. haemolytica was more frequently isolated from individual cases (87.2%) than during herd screenings (12.8%), which also stayed consistent over the sample period (p=0.74). For *M. haemolytica*, the ratio of subclinical and clinical cases did not change depending on sample origin (p=0.89, results not shown).

MIC between 2015 and 2023: Tables 2 and 3 show the distribution of minimum inhibitory concentrations (MIC), as well as MIC 50 and 90, for *P. multocida* and *M. haemolytica* against penicillin, ampicillin, amoxicillin/clavulanate, oxacillin, kanamycin/cefalexin, cefazolin, cefoperazone, cefquinome marbofloxacin, erythromycin, and pirlimycin.

Few *P. multocida* were resistant against penicillin, ampicillin, and

Table 3: Distribution of MIC, MIC50 and MIC90 for *Mannheimia haemolytica* of quarter milk samples by antimicrobial, vertical lines indicate breakpoints. The MIC50 and MIC90 (M50/90) denote the MIC where 50% and 90% of isolates were susceptible to tested antibiotics, respectively.

Antimicrobial	MIC (µg/mL)				
Penicillin	**<=0.125**	**0.25**	**>=0.5**		
	76.2% M50	14.3% M90	9.5%		
Ampicillin		**<=4**	**>16**		
		100% M50/90	-		
Amoxicillin/Clavulanate	**<=4/2**	**8/4**	**16/8**	**>=32/16**	
	92.3% M50/90	7.7%	-	-	
Oxacillin	**<=1**	**2**	**>=4**		
	38.5%	2.6%	58.9% M50/90		
Kanamycin/Cefalexin	**<=4/0.4**	**8/0.8**	**16/1.6**	**>=32/3.2**	
	56.4% M50	28.2%	15.4% M90	-	
Cefazolin	**<=4**	**8**	**16**	**>=32**	
	100% M50/90	-	-	-	
Cefoperazone	**<=2**	**4**	**8**	**>=16**	
	97.4% M50/90	-	-	2.6%	
Cefquinome	**<=1**	**2**	**4**	**>=8**	
	92.3% M50/90	7.7%	-	-	
Marbofloxacin	**<=0.25**	**0.5**	**1**	**>=2**	
	87.2% M50	7.7% M90	5.1%	-	
Erythromycin	**<=0.25**	**0.5**	**1**	**2**	**>=4**
	7.7%	2.6%	15.4%	12.8%	61.5% M50/90
Pirlimycin	**<=1**	**2**	**>=4**		
	7.7%	5.1%	87.2% M50/90		

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cefazolin. The presence of resistant *P. multocida* isolates against oxacillin, cefoperazone, and cefquinome was equally low, and the predominant MIC even decreased further from 2015 onward (p<0.01). The MIC against amoxicillin/clavulanate, kanamycin/cefalexin, and marbofloxacin increased over the years (p<0.01) - although, their MIC 50 and 90 remained below their respective breakpoints. Among the tested antimicrobials, most *P. multocida* isolates were resistant against erythromycin (81.4%) and pirlimycin (95.0%). Both MIC 50 and 90 were well above their respective breakpoints (p<0.01) (Table 2).

While only a few *M. haemolytica* isolates were resistant against penicillin, cefoperazone, or marbofloxacin, none of the tested isolates were resistant against ampicillin, amoxicillin/clavulanate, cefazolin, or cefquinome. However, *M. haemolytica* were increasingly resistant against kanamycin/cefalexin, as the MICs of 8/0.8 µg/mL and 16/1.6 µg/mL grew over the years (p<0.01). Throughout the study period, most *M. haemolytica* isolates were resistant against erythromycin (89.7%), pirlimycin (87.2%), and oxacillin (58.9%), (P< 0.001; table 3).

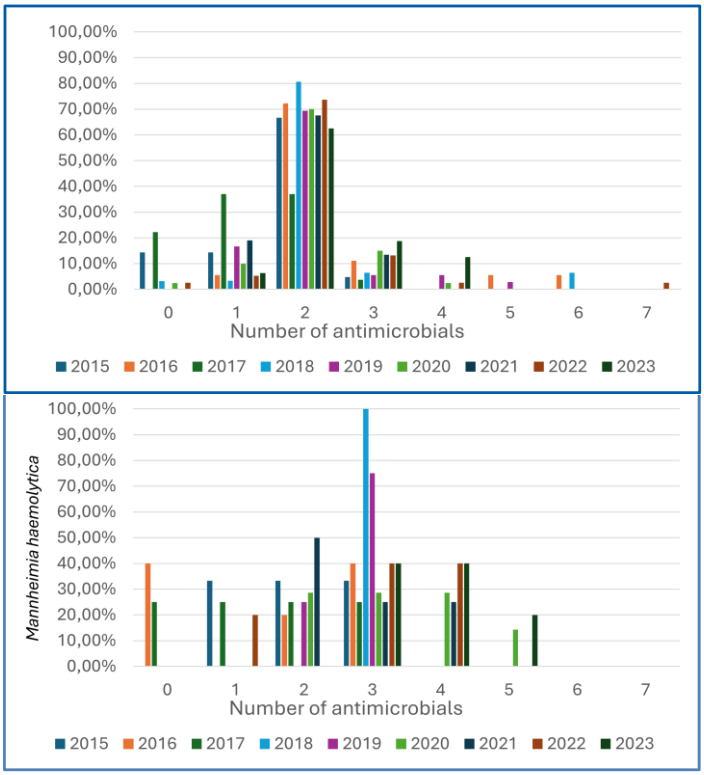

Figure 1: Number of antimicrobial substances tested that mastitis pathogen isolates tested *in-vitro* resistant to by year.

Multiple resistances: Figure 1 shows the number of isolates that were resistant against more than one antimicrobial. Most *P. multocida* isolates were resistant against two antimicrobials (67.1%, n=188), while roughly 13% were resistant to one (n=36), and 10.7% were resistant against 3 antimicrobials (n=30). Overall, only 4.3% (n=12) of *P. multocida* isolates showed no resistances, but their numbers declined over the years (p<0.01,). None of the *P. multocida* isolates was resistant against more than 7 antimicrobials at the same time.

The proportion of multi-resistant *M. haemolytica* stayed consistent from 2015 onward (p=0.59). Overall, 41% of *M. haemolytica* isolates were resistant to three (n=16), 20.5% isolates were resistant to two (n=8), and roughly 18% resistant to four antimicrobials (n=7). 7.7% of isolates were resistant to none (n=3) or one (n=3) antimicrobial, respectively, while none were resistant to more than 5 of the tested antimicrobials.

The most common combination of antimicrobials that *P. multocida* isolates were resistant against, was erythromycin and pirlimycin (n=182), which made up 67.9% of MDR by *P. multocida*. The next most common combinations were kanamycin/cefalexin, erythromycin, and pirlimycin (n=14, 5.2%) and oxacillin, erythromycin, and pirlimycin (n=11, 4.1%).

The combination of antimicrobials, that *M. haemolytica* was most commonly resistant to, was oxacillin, erythromycin, and pirlimycin (n=15), making up 41.7% of MDR by *M. haemolytica*. The second and third most common MDR were the combinations of erythromycin and pirlimycin (n=8, 22.2%) and oxacillin, kanamycin/cefalexin, erythromycin, and pirlimycin (n=4, 11.1%), respectively.

The antimicrobial both pathogens were most resistant to was pirlimycin (results not shown).

Discussion

The strength of this study is the number of samples collected over a long period of time. Both pathogens, especially *M. haemolytica,* are rarely isolated from milk samples and a continued isolation over time gives us more insight into the resistance patterns of those non-coliform Gram-negatives as mastitis pathogens.

Both *P. multocida* and *M. haemolytica* were often isolated from quarters affected with clinical mastitis. This high percentage in clinical mastitis aligned with a herd outbreak description by Barnum (1954). There, the infected quarters showed severe signs of clinical mastitis and eventually dried off completely, but none of the cows suffered systemic signs of inflammation [9]. Other studies also mention that clinical signs are very common in mastitis caused by *P. multocida* or *M. haemolytica* - with symptoms varying from abnormal milk with no macroscopical tissue damage to the infected quarter to severe clinical signs [7, 14, 15]. When looking at research on *P. multocida* and *M. haemolytica* isolated specifically from quarter milk samples, most studies report on isolated cases or herd outbreaks. In some of them, cases of shipping fever or pneumonia were documented before the mastitis cases occurred [9, 15]. However, there was no incidence in herd clustering in our data. And while the most discussed path of infection is suckling by infected calves [9, 10], we could not detect in whole herd screenings an increase in incidence of *P. multocida* or *M. haemolytica* mastitis in herds after they began using nurse cows (results not shown).

As a course of treatment, most of the isolates proved to be susceptible to penicillin and studies show that the pathogens were eliminated from the udder after treatment [7, 15]. None of those studies, however, describe the possibility of self-cure of the infected quarters, which is a phenomenon that can be frequently observed with other Gram-negative mastitis pathogens [16]. A study in Switzerland from 2023 that looked at mastitis in beef cows also found that *P. multocida* isolated from milk samples were susceptible to Penicillin, as well as Cefazolin [14], which aligns with our observations. In addition, most of the other MIC reported by Vollweider (2023) also coincided with ours. However, the MIC 90 against oxacillin and kanamycin/cefalexin was still below the respective breakpoint in our study, while the MIC 90 reported by Vollweider (2023) were above those breakpoints. Some antimicrobials were not included in our study, but isolates in other studies were frequently resistant to the following antimicrobials: tetracycline, chloramphenicol, neomycin, streptomycin spiramycin, and sulfonamides [7, 14]. Studies about AMR of bovine *P. multocida* and *M. haemolytica* from different sources often reported similar resistance patterns, especially when the data derived from the same geographic regions [11, 17]. Especially studies from Germany also reported low resistances toward penicillin, with isolates being the most resistant against spectinomycin and tetracycline, amongst other antimicrobials that differed in between studies [8, 11, 17].

P. multocida was largely resistant against erythromycin and pirlimycin in our study. Consequently, a large percentage of isolates also showed multidrug resistance (MDR) against those two antimicrobials. In the same manner, the majority (41%) of *M. haemolytica* isolates showed MDR against three antimicrobials, those antimicrobials being oxacillin,

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erythromycin, and pirlimycin. Different studies on isolates from quarter milk samples, as well as samples from BRD report a rising incidence in MDR [7, 17], especially for *P. multocida* [11]. Again, MDR were different depending on the geographic regions.

These resistances may be explained by different resistance genes, that can often be transferred between pathogens [17]. A resistance against macrolides has been described in multiple studies from varying regions, in both *P. multocida* and *M. haemolytica*, caused by macrolide-resistance-genes erm(42), mph(E), and msr(E), expressed in different combinations [18, 19], as well as the mef(C) and mph(G) genes [20]. According to Desmolaize et al. (2011), two of the types of macrolide resistance coincide with a resistance against lincosamides [18], explaining the resistances of *P. multocida* and *M. haemolytica* isolates in this study against both erythromycin and pirlimycin. Though only shown here by *M. haemolytica* isolates, resistances against beta-lactams and aminoglycosides (especially kanamycin) have been described in other studies as well [8, 19, 20].

Despite the very clinical presentation and high incidence of MDR of mastitis due to *P. multocida* and *M. haemolytica*, the therapy seemed to be surprisingly simple. Although the resistances vary throughout different regions, in Germany at least penicillin only showed very few resistances. Unfortunately, the number of studies on mastitis by *P. multocida* and *M. haemolytica* is sparse and the question of self-cure remains. Whether antimicrobial therapy is completely necessary or if the pathogens would still be eliminated from the infected quarter, if untreated, ultimately has no conclusive answer at this point in time. In the end, the decision of treatment has to be left up to the practicing veterinarian in those rare cases.

Conclusion

In conclusion, roughly equal numbers of isolates originated from individual cases as herd sampling and were largely isolated from cases of clinical mastitis, especially *M. haemolytica*. *In-vitro* resistances remained mostly similar throughout the years, with *P. multocida* being largely *in-vitro* resistant against erythromycin and pirlimycin, and *M. haemolytica* against oxacillin, kanamycin/cefalexin, erythromycin, and pirlimycin, while both were over 90% sensitive to the other antimicrobials tested. Although the theory of spontaneous self-cure has yet to be explored, if antimicrobial treatment were elected, penicillin seemed to be the antimicrobial of choice.

Disclosure of conflicts of interest

The authors declare no potential conflicts of interest.

Compliance with Ethical Standards

This retrospective study used data from routine diagnostic samples and has been conducted in compliance with ethical standards.

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