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Emergence of Resistance to Macrolides and Rifampin in Clinical Isolates of *Rhodococcus equi* from Foals in Central Kentucky, 1995 to 2017

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ABSTRACT The objective of this study was to determine the prevalence of *Rhodococcus equi* strains resistant to macrolides and rifampin over time in clinical samples from foals submitted to diagnostic laboratories in central Kentucky. We performed a retrospective observational study of all clinical samples from foals that were submitted to veterinary diagnostic laboratories in Kentucky between January 1995 and December 2017. Samples were included if the *R. equi* bacterium was cultured and tested for *in vitro* susceptibility to erythromycin or rifampin. *In vitro* susceptibility testing to erythromycin was available for 2,169 isolates of *R. equi*, while susceptibility testing to both erythromycin and rifampin was available for 1,681 isolates. Rifampin resistance was first detected in 2000, and erythromycin resistance was first detected in 2004. Between 1995 and 2006, the proportion of resistant isolates of *R. equi* was 0.7% for erythromycin and 2.3% for rifampin. There was a significant ($P < 0.001$) increase in the proportion of resistant *R. equi* between 2007 and 2017, with 13.6% of isolates being resistant to erythromycin and 16.1% being resistant to rifampin. Between 2007 and 2017, isolates of *R. equi* resistant to erythromycin or rifampin were significantly less likely to be isolated from feces than from the respiratory tract, other soft tissues, or musculoskeletal infections. The considerable increase in the prevalence of isolates of *R. equi* resistant to macrolides and rifampin since 2007 is of concern for both human and animal health.

KEYWORDS azithromycin, clarithromycin, erythromycin, foal, horse, pneumonia

Rhodococcus equi, a Gram-positive facultative intracellular pathogen, is one of the most important causes of disease in foals and a common opportunistic pathogen in immunocompromised humans (1, 2). In either host, infection is most commonly characterized by life-threatening pyogranulomatous pneumonia, although infections at other sites are not uncommon (2, 3). The combination of a macrolide (erythromycin, azithromycin, or clarithromycin) and rifampin has been the mainstay of therapy in foals infected with *R. equi* since the early 1980s, with, until recently, only isolated reports of resistance (4–6). Macrolide antimicrobial agents and rifampin are also used commonly for the treatment of infections caused by *R. equi* in humans (2).

Although *R. equi* can be cultured from the environment of virtually all horse farms, the clinical disease in foals is sporadic at some farms but endemic at others. In the absence of effective preventive measures, the control of infections caused *R. equi* at many farms where the disease is endemic has relied on early the detection of subclin-

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ical pulmonary disease using thoracic ultrasonography and an initiation of treatment with antimicrobial agents prior to development of clinical signs (7). This approach might have decreased mortality due to *R. equi* pneumonia at some farms, although controlled studies are lacking (7). However, one controlled clinical trial at an endemic farm demonstrated that many foals with subclinical pulmonary lesions recover without treatment and that the treatment of foals with subclinical pulmonary lesions with azithromycin and rifampin did not accelerate recovery compared with an untreated group, indicating that a mass antimicrobial treatment of all foals with subclinical lesions was unnecessary at that farm (8). Moreover, ultrasonographic screening has resulted in a considerable increase in antimicrobial drug use at horse farms because a large proportion of foals have subclinical pulmonary lesions without developing clinical signs (9). In one study, it was documented that approximately 40% of isolates of *R. equi* from pneumonic foals at 1 farm were resistant to all macrolides and rifampin approximately 7 years after the initiation of an ultrasonographic screening program and the resulting treatment of all foals with subclinical pulmonary lesions. However, it is unknown if macrolide and rifampin resistance is an issue isolated at that particular farm or if it is widespread. The increasing resistance of bacteria to macrolides and rifampin extends beyond equine rhodococcus infection since these drugs are widely used in humans for the treatment of tuberculosis (rifampin) and respiratory tract, skin, and genital tract infections (macrolides).

The main objective of this study was to determine the prevalence of *R. equi* strains resistant to macrolides and rifampin over time in clinical samples from foals submitted to diagnostic laboratories in central Kentucky. We show that the frequency of macrolide or rifampin resistance was relatively low until 2006. There was a significant increase in the proportion of resistant *R. equi* between 2007 and 2017, with 13.6% of isolates being resistant to erythromycin and 16.1% being resistant to rifampin.

RESULTS

In vitro susceptibility testing to erythromycin was available for 2,169 isolates of *R. equi*, while susceptibility data for both erythromycin and rifampin were available for 1,688 isolates. *In vitro* susceptibility data for azithromycin and clarithromycin were only available between 2002 and 2011, depending on the laboratory. Therefore, only erythromycin was used to assess *R. equi* susceptibility to macrolides over time. Of the 2,169 total isolates, 1,989 (91.7%) originated from Kentucky, 69 (3.2%) from Louisiana, 30 (1.4%) from New York, 27 (1.2%) from Oklahoma, 17 (0.8%) from Indiana, and 37 from one of 11 other states. The most common sample type was tracheobronchial aspirate ($n = 955$) followed by lung tissue ($n = 578$; 44%), other soft tissues ($n = 240$; 11.1%), feces ($n = 133$; 6.1%), and musculoskeletal infections ($n = 120$; 5.5%). Sample type was not reported for 143 (6.6%) isolates.

The first occurrence of rifampin resistance was detected in 2000, and erythromycin resistance was first detected in 2004. Isolates resistant to rifampin originated from Kentucky ($n = 203$), New York ($n = 13$), Louisiana ($n = 3$), Oklahoma ($n = 2$), Indiana ($n = 1$), North Carolina ($n = 1$), Texas ($n = 1$), and Virginia ($n = 1$). Isolates resistant to erythromycin originated from Kentucky ($n = 171$), Louisiana ($n = 21$), New York ($n = 9$), Oklahoma ($n = 1$), and Virginia ($n = 1$). Between 1995 and 2006, the proportion of resistant *R. equi* isolates was 0.7% for erythromycin and 2.3% for rifampin (Fig. 1). There was a significant ($P < 0.001$) increase in the proportion of resistant *R. equi* between 2007 and 2017, with 13.6% of isolates being resistant to erythromycin and 16.1% being resistant to rifampin (Fig. 1). Using logistic regression, there was a significant effect of time period ($P < 0.001$) and sample type ($P = 0.002$ for erythromycin and $P = 0.032$ for rifampin) on the proportion of isolates of *R. equi* resistant to erythromycin or rifampin, but the effect of laboratory was not statistically significant. After adjusting for laboratory and sample type, the odds of detecting erythromycin-resistant isolates between 2007 and 2017 was 20.7 (95% confidence interval [CI], 8.4 to 51.1; $P < 0.001$) times higher than between 1995 and 2006. For rifampin, the odds of detecting a resistant

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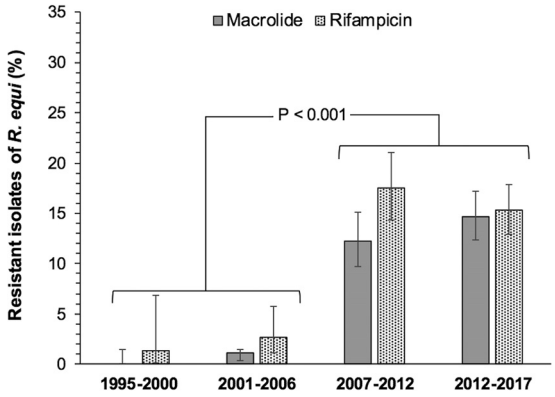

FIG. 1 Proportion (percentages and 95% exact binomial confidence intervals) of clinical isolates of *R. equi* resistant to macrolides or rifampin for time periods 1995 to 2000 ($n = 260$ for macrolides, $n = 80$ for rifampin), 2001 to 2006 ($n = 465$ and 260, respectively), 2007 to 2012 ($n = 614$ and 260, respectively), and 2013 to 2017 ($n = 839$ and 837, respectively). Data were collected from 3 veterinary diagnostic laboratories in Kentucky.

isolate between 2007 and 2017 was 7.7 (95% CI, 3.7 to 16.1; $P < 0.001$) times higher than between 1995 and 2006.

The proportion of isolates of *R. equi* resistant to erythromycin or rifampin for each type of sample is presented in Table 1. Between 1995 and 2006, the odds of detecting isolates of *R. equi* resistant to erythromycin or rifampin was not significantly different between sample types. Between 2007 and 2017, the odds of detecting isolates of *R. equi* resistant to rifampin in tracheobronchial aspirate, lung, soft tissue, and musculoskeletal samples was significantly higher than in feces. Similar results were obtained for macrolide resistance, except that the odds of detecting macrolide-resistant isolates in lung tissue was not significantly higher than in feces ($P = 0.080$).

Of the 1,681 total isolates for which susceptibility results were available for both erythromycin and rifampin, 1,412 (84%) were susceptible to both drugs, 154 (9.2%) were resistant to both drugs, 71 (4.2%) were susceptible to erythromycin and resistant to rifampin, and 44 (2.6%) were susceptible to rifampin but resistant to erythromycin. The results of *in vitro* susceptibility testing to azithromycin, clarithromycin, and erythromycin were available for 925 isolates. There was almost perfect agreement (kappa,

TABLE 1 Proportion of isolates of *R. equi* resistant to macrolides or rifampin by site of collection and time period[a]

Drug and site of collection	No. (%) of isolates collected in:	
	1995–2006	2007–2017
Macrolides		
Tracheobronchial aspirate	4/313 (1.3)	113/642 (17.6)[b]
Lung	1/350 (0.3)	23/228 (10.1)[c]
Musculoskeletal	0/23 (0)	11/97 (11.3)[b]
Soft tissue	0/11 (0)	32/229 (14.0)[b]
Feces	NA[d]	1/133 (0.8)
Rifampin		
Tracheobronchial aspirate	7/312 (2.2)	104/628 (15.6)[b]
Lung	NA	24/134 (17.9)[b]
Musculoskeletal	1/21 (4.8)	17/95 (17.9)[b]
Soft tissue	0/7 (0)	43/227 (18.9)[b]
Feces	NA	1/133 (0.8)

[a]Data were collected between 1995 and 2017 from 3 veterinary diagnostic laboratories in Kentucky.
[b]Significantly higher proportion of resistant isolates than feces for years 2007 to 2017 ($P < 0.05$).
[c]Tendency toward a higher proportion of resistant isolates relative to feces for years 2007 to 2017 ($P = 0.080$).
[d]NA, not applicable.

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0.81; $P < 0.001$) between the 3 drugs for the detection of susceptibility or resistance to macrolides.

DISCUSSION

In this report, we demonstrate a drastic increase in the proportion of *R. equi* isolates from foals resistant to macrolides or rifampin over time. The emergence of bacterial resistance to macrolides and rifampin, the most heavily relied upon antimicrobial agents for the prophylaxis and treatment of infections caused by *R. equi* in foals, is of profound concern to the horse breeding industry. These antimicrobial agents are also categorized as critically important for human medicine by the World Health Organization (10). Given that *R. equi* is not infrequently associated with opportunistic infections in humans (2), the emergence of macrolide and rifampin resistance might also adversely impact human health.

During the introduction of the combination of a macrolide and rifampin for the treatment of infections caused by *R. equi* in foals in the 1980s and the early 2000s, resistance to rifampin was extremely rare, and there was only one report of resistance to a macrolide (4–6). In a more recent study, 12 of 328 (3.7%; 95% CI, 1.9% to 6.3%) isolates of *R. equi* cultured from foals in Texas and Florida between 1999 and 2008 were resistant to macrolides and rifampin. These results are in line with our study's results. If, by analyzing our data, we consider the same time period (from 1999 to 2008), 20 of 780 (2.6%; 95% CI, 1.6 to 3.9%) isolates were resistant to macrolides and 25 of 369 (6.8%; 95% CI, 4.4% to 9.8%). The present study demonstrates that the proportion of resistant isolates has increased further since then in Kentucky. Additional studies will be required to determine if the same increase over time has occurred in other states in the United States and in other countries.

The practice of ultrasonographic screening for the early identification and mass treatment of pneumonic foals was first described in 2001 and was implemented at several farms in the following years (7). The temporal association between this widespread use of macrolides and rifampin resulting from this practice and the subsequent increase in the frequency of detection of resistant isolates documented in this study leads to the hypothesis that there might be a causal relationship. Additional studies will be required to test this hypothesis experimentally because the screening status of the farm of origin was unknown in this retrospective study.

In this study, there was an almost perfect agreement between the *in vitro* susceptibility to azithromycin, clarithromycin, and erythromycin. This is not surprising given that macrolide resistance in *R. equi* is typically the result of expressing *erm*(46), which confers resistance to all macrolides, lincosamides, and streptogramin B. (11) Due to the retrospective nature of this study, resistant isolates were not available to test for the presence of *erm*(46). This gene is transferable easily from resistant to susceptible strains of *R. equi* by conjugation, which might have contributed to the increase in the prevalence of macrolide resistance over time documented herein. The majority (77.8%) of macrolide-resistant isolates in this study were also resistant to rifampin. Rifampin resistance in *R. equi* is the result of mutations in the *rpoB* gene, and there are no known mechanisms of cross-resistance between macrolides and rifampin (4, 6, 12). The selection pressure caused by the combined use of rifampin with macrolide for the prevention and treatment of *R. equi* infection in foals might have coselected for the acquisition of *erm*(46) along with *rpoB* mutations.

The proportion of isolates resistant to macrolides or rifampin was similar for all types of samples, with the exception of feces, for which the frequency of resistance was much lower. *R. equi* is a soil saprophyte that can be detected in the feces of most healthy horses. Virtually all isolates of *R. equi* causing disease contain a large plasmid (designated pVAPA), and plasmid-cured derivatives are avirulent for foals (13). Although *erm*(46) is not typically carried on pVAPA, the majority of macrolide- and rifampin-resistant isolates of *R. equi* identified in previous studies contain pVAPA (11, 14). Conversely, most isolates from soil or feces do not contain pVAPA and are avirulent. It is likely that the lower frequency of resistant isolates in feces is due to the fact that most

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fecal isolates are avirulent and reflect the presence of *R. equi* in the environment. However, this hypothesis cannot be tested because the molecular detection of pVAPA was not performed.

This study has several important limitations inherent to its retrospective observational design. The collection and submission of diagnostic samples for culture and susceptibility were not systematic and randomized. The possibility that selection bias due to an increased awareness to the problem of antimicrobial resistance in *R. equi* contributed to the increase in the prevalence of resistance over time cannot be ruled out. Another important limitation is that only qualitative susceptibility data were available for the entire study period. As a result, changes in MICs over time could not be evaluated. Finally, the outcomes of most foals from which samples were collected were unknown. Therefore, we could not determine if there is an association between the detection of a resistant isolate and the outcome. In a prior study, the odds on nonsurvival for foals infected with isolates of *R. equi* resistant to macrolides and rifampin was approximately 7 times that for foals infected with susceptible isolates (14).

MATERIALS AND METHODS

Data collection. The records of the 3 main diagnostic laboratories processing clinical samples from foals housed at farms in Kentucky were solicited and accepted to participate to the study. The laboratories were Hagyard Equine Medical Institute Diagnostic Laboratory, Rood & Riddle Equine Hospital Diagnostic Laboratory, and University of Kentucky Veterinary Diagnostic Laboratory, all located in Lexington, KY. The records of clinical samples from foals submitted between January 1995 and December 2017 were reviewed. Records prior to 2006 could not be retrieved for one laboratory. Samples were included in this study if *R. equi* was cultured and tested for *in vitro* susceptibility to erythromycin or rifampin. Isolates were identified as *R. equi* based on colony morphology; a positive CAMP test; and biochemical profile test results as catalase positive, oxidase negative, urease negative, and glucose fermentation negative. For each isolate, data collection included year of submission; state of origin; sample type; method of *in vitro* susceptibility testing used; as well as *in vitro* susceptibility testing results for erythromycin, rifampin, and, when available, azithromycin and clarithromycin.

***In vitro* susceptibility testing.** Two laboratories used the disk diffusion susceptibility method exclusively and one laboratory used disk diffusion until 2010 and broth microdilution (Trek Sensititer; Thermo Fisher Scientific, Grand Island, NY, USA) thereafter. Disk diffusion and broth microdilution were performed in accordance to the guidelines established by the Clinical and Laboratory Standard Institute (CLSI) (8). Control strains used to validate the assay weekly were *Staphylococcus aureus* ATCC 25923, *S. aureus* ATCC 29213, *Streptococcus pneumoniae* ATCC 46619, *Enterococcus faecalis* ATCC 29212, and *Escherichia coli* ATCC 25922.

There are currently no CLSI-approved interpretive criteria for the susceptibility testing of *R. equi* in humans or horses. Thus, CLSI interpretive criteria for *Staphylococcus aureus* were used by all 3 laboratories, as widely reported by veterinary diagnostic laboratories and in the literature (14–17). Susceptibility was defined as a zone of inhibition of $\geq$18 mm or an MIC of $\leq$2 mg/liter for azithromycin and clarithromycin, $\geq$23 mm or $\leq$0.5 mg/liter for erythromycin, and $\geq$20 mm or $\leq$1 mg/liter for rifampin. For the purpose of this study, all nonsusceptible isolates (i.e., isolates reported as intermediate or resistant) were considered resistant. This decision was based on the fact that virtually all isolates of *R. equi* in prior studies had MICs for azithromycin, clarithromycin, erythromycin, and rifampin well below the susceptibility breakpoints listed above (12, 16). In addition, some strains of *R. equi* positive for *erm*(46) and, therefore, known to be macrolide resistant have MICs that would be considered of intermediate susceptibility using the interpretive criteria for *S. aureus* (11).

Data analysis. Year was dichotomized as 2 approximately equal time periods (1995 to 2006 and 2007 to 2017) for data analysis. Sample types were grouped as tracheobronchial aspirates, lung tissue, musculoskeletal infections (bone, cartilage, or synovial fluid), soft tissue (lymph nodes, blood, abdominal abscesses, eyes, wounds, or internal organs other than the lungs), or feces. The proportion of isolates of *R. equi* resistant to erythromycin or rifampin was compared between the 2 time periods using the Fisher's exact test. Multivariable logistic regression was used to calculate the adjusted odds ratio for the potential association between time period and resistance to erythromycin or rifampin after adjusting for sample type and laboratory. Model fit was assessed using the Hosmer and Lemeshow test and Akaike's information criterion. Agreement between susceptibility or resistance to azithromycin, clarithromycin, and erythromycin was assessed using the kappa statistic. The strength of agreement can be categorized as slight (kappa, 0 to 0.2), fair (0.21 to 0.4), moderate (0.41 to 0.60), substantial (0.61 to 0.80), or almost perfect (0.81 to 1.0) (18). For all analysis, $P < 0.05$ was considered statistically significant.

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We declare no conflict of interest.

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