Comparative Effectiveness of Sustained-Release Moxidectin (ProHeart 6) and Ivermectin (Heartgard Plus) for the Prevention of Heartworm Infection in Dogs in the United States

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ABSTRACT

This nationwide, post-marketing, epidemiological study using >11 million electronic medical records for dogs visiting >500 Banfield veterinary hospitals indicates that both moxidectin and ivermectin are highly effective for the prevention of heartworm infection in dogs. As expected, however, the 100% effectiveness reported for both drugs in limited pre-clinical laboratory studies with experimentally induced infections and field trials with client-owned dogs was not attained. Once chemoprophylaxis is discontinued, the residual effectiveness of moxidectin lasts significantly longer than for ivermectin. This finding is particularly important for protection of dogs living in heartworm endemic areas where *Dirofilaria immitis* transmission occurs year-round and where owner non-compliance is a greater problem with oral monthly drug administration than with sustained-release drug formulations.

INTRODUCTION

Heartworm infection in dogs is caused by

the mosquito-borne filarial nematode *Dirofilaria immitis*, which typically inhabits the right ventricle and pulmonary arteries. Canine heartworm infection has been diagnosed in all 50 of the United States, but it is endemic especially in the southern states along the Gulf Coast, the Atlantic seaboard, and the Mississippi River basin where temperatures are favorable for mosquito breeding.[1] Canine heartworm infection is preventable if puppies begin chemoprophylaxis no later than 8 weeks of age.[2] Chemoprophylaxis is intended not only to protect individually treated dogs, but also to lower the prevalence of infection and worm burdens among dogs in a community, thereby decreasing the risk of mosquito transmission to dogs that are not on heartworm chemoprophylaxis. The American Heartworm Society notes that in regions where heartworm transmission occurs during most of the year, seasonal chemoprophylaxis may not be the most effective method, since year-round treatment is preferred in order to enhance owner compliance with drug administration.[2] Lack of compliance is recognized to be a serious problem throughout the country.

Heartworm infections can be prevented by the use of oral, topical, and parenteral formulations that can be administered daily, monthly, or every 6 months. The most widely used heartworm preventives are the macrocyclic lactones, particularly ivermectin. Ivermectin has a very high therapeutic/toxic ratio and has activity against microfilariae, third and fourth stage larvae, and in some instances young adult heartworms. Based on extensive laboratory testing and limited field trials, ivermectin is considered nearly 100% effective against *D. immitis* when administered orally at the prescribed dose at monthly intervals.[2] In addition, the extended retroactive efficacy of the macrocyclic lactones provides additional protection in the event of owner noncompliance (ie, inadvertent delay or omission of a regularly scheduled dose).[3]

In June 2001, a subcutaneously injected slow-release formulation of moxidectin-impregnated, lipid microspheres (ProHeart 6, Fort Dodge Animal Health, Fort Dodge, IA) became available with an indication to prevent *D. immitis* infection for 6 months and to treat existing larval and adult stages of the canine hookworm Ancylostoma caninum. The American Heartworm Society noted that information not presently in the public domain about the post-treatment effectiveness of ProHeart 6 indicates that full protection probably extends beyond 6 months when administered at the recommended dose.[2] Effectiveness of ProHeart 6 in experimentally infected mongrel dogs showed that a single subcutaneous injection at the recommended dosing rate appeared to completely protect adult dogs against experimental challenge inoculation with infective third-stage larvae of *D. immitis* for a period of 12 months.[4] The sustained-release formulation of moxidectin was voluntarily removed from the market by the manufacturer in the United States in September 2004 for questions related mainly to safety, but it remains on the market in other countries including Canada, Italy, and Australia. Approximately 1 year after ProHeart 6 was voluntarily recalled, a study using almost 7 million medical records for nearly 2 million individual dogs in the United States found that the safety profile of ProHeart 6 was comparable to orally administered ivermectin for heartworm prevention except that monthly ivermectin administration was associated with a small but statistically significant increased risk of death.[5]

Despite the availability of safe and effective drugs to prevent canine heartworm infection, a survey of veterinarians conducted by Merial Limited and the American Heartworm Society showed that more than 240,000 dogs tested positive for heartworm infection in 2001. Another survey of veterinarians conducted in 2003 by Novartis Animal Health U.S. Inc. revealed that three fourths of the veterinarians surveyed recommend year-round heartworm prevention for dogs, but only half of the pet owners followed their veterinarian's

recommendations.[6] The large number of reported positive heartworm tests for dogs may reflect failure to recommend or use available heartworm prophylactic drugs by veterinarians and pet owners, respectively, inappropriate use (lack of compliance) of available drugs, or lack of drug effectiveness. The Food and Drug Administration Center for Veterinary Medicine (FDA CVM) reported that by December 2005, it had received 5,794 reports of lack of effectiveness for heartworm preventive drugs.[7] They speculated this large number of reported drug failures for products designed to prevent heartworm disease in dogs could be due to an increased concern among veterinarians and pet owners about heartworm prevention effectiveness, owners improperly administering the drugs, or a problem with the products. Their analysis determined that 1,301 reports were definitely related to failure of the products since they reportedly had been administered according to the label, there was a proper purchase history, and a negative heartworm antigen test had been performed prior to initiation of the drug and at least 7 months after beginning prevention, followed by a positive antigen test. This large number of purported drug failures may also be due in part to methods of determining lack of effectiveness, as well as to dog owners switching to oral, monthly ivermectin when ProHeart 6 was voluntarily recalled. In 2005, the FDA CVM's Division of Surveillance asked the sponsors of all marketed heartworm prevention products to refrain from claiming 100% effectiveness in promotion and advertising.

Although the effectiveness of heartworm preventive products has been assumed to be nearly 100% based on limited experimental studies with induced infections in the laboratory and field trials on client-owned animals, large post-marketing studies to determine the effectiveness of heartworm preventives under natural conditions have not been conducted. Failures that occurred during intended normal use were generally attributed to lack of owner compliance or relocation of unprotected dogs from areas free of heartworm transmission to enzootic areas. The purpose of the present study, therefore, was to estimate the effectiveness of parenterally administered, sustained-release moxidectin (moxidectin SR) and orally administered ivermectin (Heartgard Plus, Merial Animal Health, Athens, GA) compared with no heartworm preventive therapy.

METHODS

Banfield the Pet Hospital operates a national network of >500 full-service primary care veterinary hospitals located in 44 states. Banfield currently cares for approximately 80,000 pets per week, of which approximately 50,000 are dogs, and uses proprietary software (PetWare®) to create standardized electronic medical records that are uploaded nightly to a data warehouse where they are stored in Oracle (Redwood Shores, Calif) format. Medical records of 11,699,672 office visits for dogs seen at 517 Banfield hospitals operating during the period from January 1, 2002 to December 31, 2005 were transferred to Purdue University as pipe-delimited ASCII files and were converted into SAS format (SAS Inc, Cary, NC) for analysis.

Medical records included in the study were categorized as follows: (1) visits for dogs that had received only moxidectin SR for heartworm prophylaxis after the age of 6 months but these dogs could have received ivermectin before the age of 6 months; (2) visits for dogs that had received only ivermectin (Heartgard Plus, Merial Animal Health, Athens, GA) for heartworm prophylaxis and never received moxidectin SR; and (3) visits for dogs that had never received any type of heartworm prophylaxis. All other dog visits were excluded from this study. The proportion of dogs in each of the 3 groups was determined by age (<1, 1 to 3, 4 to 8, >8 years), body weight (≤25, 26 to 50, 51 to 75, 76 to 100, >100 lbs), gender (female, male) and neuter status (intact, neutered), breed (mixed, pure), and geo-

graphic risk of heartworm exposure (high, low, moderate), based on observed heartworm infection rates. Geographic areas were considered low, moderate, or high risk if antigen positive test rates were 0% to <0.5%, 0.5% to 1.25%, and >1.25%, respectively. Multivariable logistic regression analysis was used to examine the likelihood of *D. immitis* infection for dogs having received moxidectin SR versus ivermectin and for the risk of an antigen positive test for dogs on heartworm preventive versus no preventive.

Two measures of the effectiveness of heartworm prevention were calculated, namely the effectiveness of chemoprophylaxis while a dog was under the labeled protection period of the particular drug (treatment effectiveness) and the effectiveness of chemoprophylaxis after a dog was no longer under the labeled protection period of the drug or its use was discontinued (residual treatment effectiveness). For example, if a tablet of ivermectin was dispensed, the protection period was assumed to be 1 month; if a 6-dose card of ivermectin was dispensed, the protection period was assumed to be 6 months. If a 6-dose card of ivermectin was dispensed and another 6-dose card was dispensed 5 months later, the protection period was assumed to be 12 months from the time the first 6-dose card was dispensed. Although owner compliance failure is considered to be relatively high, particularly with oral and topical products, it is virtually impossible to determine. Thus, the assumption was made that the products were administered according to the instructions for the product. Also, it was assumed that owners did not purchase monthly products from other sources. An injection of moxidectin SR assumes a protection period of 6 months following administration. Furthermore, protection was assumed to continue over gaps between product coverage of up to 1 month and for 1 month at the end of heartworm treatment coverage. Another assumption underlying this study and a previous safety study of moxidectin SR and ivermectin using Banfield medical records[5] is that the first dose of the oral, monthly heartworm preventives was administered to the dogs on the same day of the office visit in which they appeared in the medical record. If such was not the case for ivermectin because of owner non-compliance, it would probably be reflected in a lower rate of treatment effectiveness when compared with moxidectin SR as well as increased residual effectiveness if administration was delayed.

For the purposes of analysis, a heartworm protection period begins at a date A and ends at a date B and satisfies the following conditions:

1) The dog was given one and only one type of heartworm preventive during the protection period
2) The dog had never been under the protection of an alternative preventive prior to the protection period with the exception that dogs on moxidectin SR could have received ivermectin prior to 6 months of age
3) The protection period begins at the earlier of:
    a) The date a negative antigen test was obtained and the dog was under the protection of the heartworm preventive at the time of the negative antigen test or the negative antigen test was obtained no more than 1 month prior to the dog being under this heartworm preventive
    b) The date the dog was started on heartworm preventive if the dog was 0 to 3 months of age
4) The protection period ends when any of the following occur:
    a) The dog was no longer protected under the heartworm preventive
    b) The dog was given an alternative heartworm preventive
    c) A positive antigen test was obtained
    d) The study period ended
    e) The dog died
5) If a dog was never given a heartworm

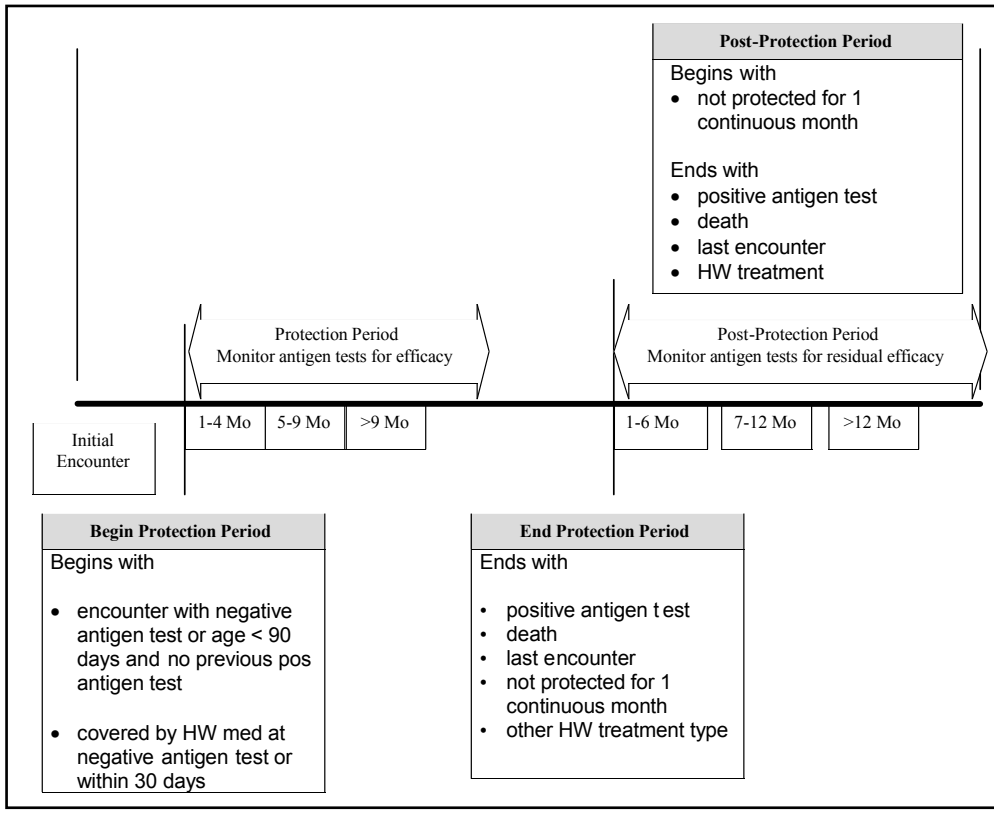
preventive during the study period, then a heartworm protection period begins at first encounter in which age is ≥3 months of age or at the first negative antigen test and the protection period is denoted as having treatment type "none"

A schematic summarizing the beginning and end of the protection periods is shown in Figure 1.

If a dog had multiple heartworm protection periods, only the first qualifying period was included in the effectiveness analyses. Banfield guidelines recommend that all dogs have a negative antigen test within 1 month before starting on heartworm chemoprophylaxis and be retested yearly. Banfield veterinarians recommend that dogs <6 months of age be placed on ivermectin while dogs ≥6 months of age be administered moxidectin SR provided they first have a negative heartworm antigen test.

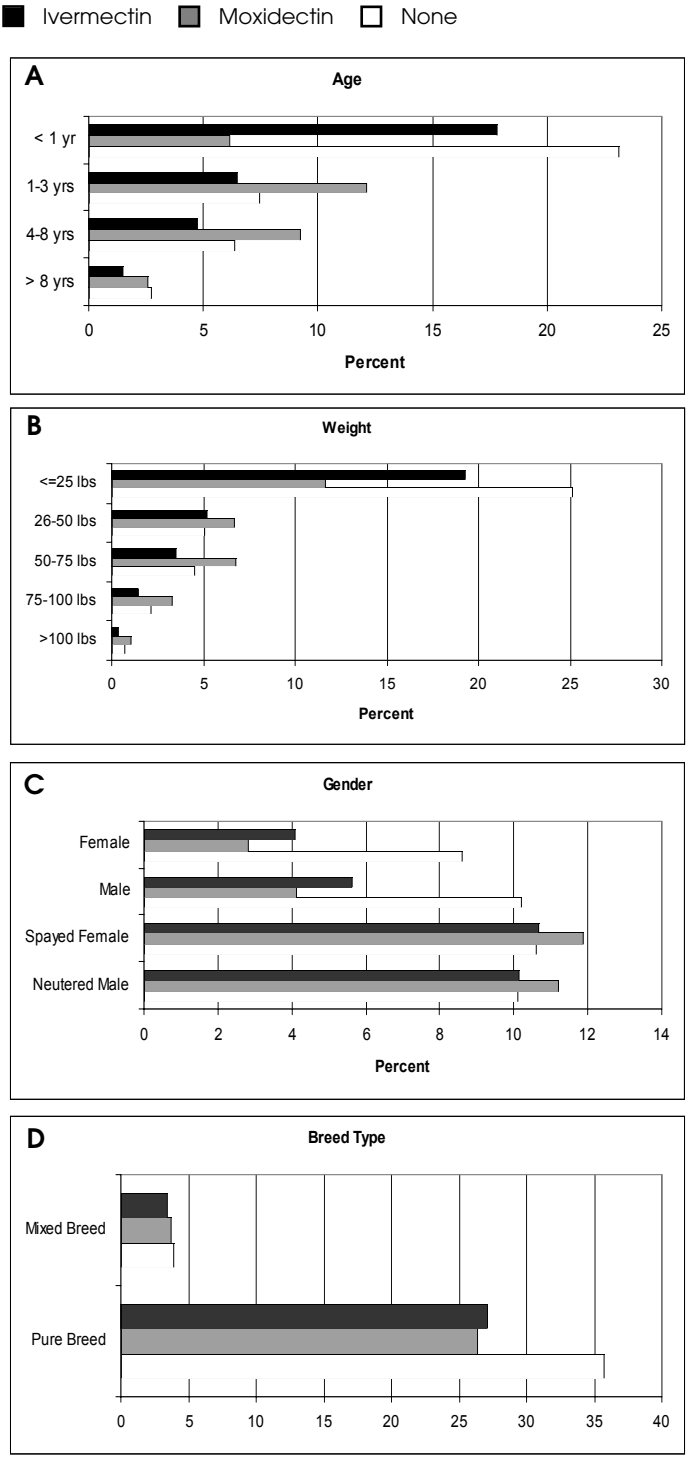
After this study began, the American Heartworm Society published guidelines recommending that antigen testing be performed prior to starting preventive heartworm therapy and if antigen negative, the dog should be tested again 4 and 9 months later.[2] However, only if a dog is positive after 9 months under preventive and the previous antigen tests were negative should product failure be considered as the most likely reason for infection. This criterion for product failure was used in the present study. All heartworm antigen testing performed by Banfield veterinarians was with the SNAP® Heartworm Antigen test (IDEXX Laboratories Inc, Westbrook, Mass). Any positive antigen test was considered as evidence of heartworm infection. The term moxidectin SR as used in this study indicates ProHeart 6 was administered by injection while the term ivermectin indicates Heartgard Plus was administered orally.

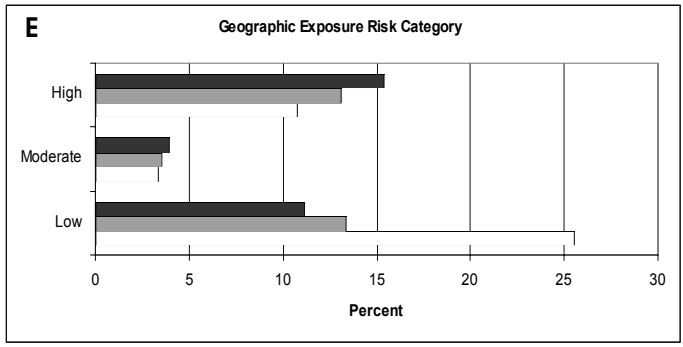
Figure 1. Schematic of the protection and post-protection periods that were used to evaluate the effectiveness of ivermectin and moxidectin SR for the prevention of heartworm infection in dogs.



For analyses of both the treatment effectiveness and the residual treatment effectiveness, heartworm infection rates with their 95% confidence limits were calculated based on the number of positive antigen tests divided by the total number of antigen tests performed multiplied by 1,000, during the study period. Multivariable logistic regression was used to calculate the risk of a dog having an antigen positive test during various months of the protection or post-protection period as a function of heartworm preventive type, while controlling for heartworm exposure level, age, body weight, gender, breed type and neuter status. All 2-way interactions were evaluated and if significant, these interactions were shown in the regression models by characterizing risk for different levels of the interacting variables. Risk was expressed as an odds ratio with 95% confidence limits. Multivariable logistic regression models were developed using SAS version 9.1.3 software with the PROC LOGISTIC procedure. A P value <0.05 was considered statistically significant. The percent protection provided by a specific heartworm preventive was calculated as the (incidence of a positive antigen test at >9 months following start of a protection period among dogs receiving no heartworm

Figure 2. Proportion of dogs that were administered ivermectin (N = 250,592), moxidectin SR (N = 222,498), or no heartworm preventive (N = 305,265) at Banfield the Pet Hospital from January 1, 2002 to December 31, 2005. **A:** Age; **B:** Weight; **C:** Gender and neuter status; **D:** Breed type; **E:** Geographic exposure risk level.





preventive minus the incidence of a positive antigen tests at >9 months of a protection period among dogs receiving a specific heartworm preventive) ÷ by the (incidence of a positive antigen test at >9 months among dogs receiving no heartworm preventive) × 100.

RESULTS

The proportion of dogs that received ivermectin (n = 250,592), moxidectin SR (n = 222,498), or no heartworm preventive (n = 305,265) is shown in Figure 2 as a function of their age, body weight, gender and neuter status, breed, and geographic risk of heartworm exposure. Gender and breed type were not consistently associated with use of either drug while neutered dogs were more likely to receive moxidectin SR than ivermectin compared with intact dogs, regardless of their exposure status (Table 1). However, the magnitude of this disparity was small ranging from 4% (odds ratio = 1.04) in the high exposure group to 14% (odds ratio = 1.14) in the low exposure group. In general, older and larger dogs were significantly more likely to have received moxidectin SR than ivermectin compared with younger and smaller dogs probably as a result of Banfield's suggested policy for use of ivermectin in puppies <6 months of age.

The rate of antigen positive tests was generally low for all dogs receiving heartworm preventive regardless of whether a dog lived in a high or low exposure area, whereas the rates were significantly higher for dogs not receiving any heartworm preventive (Table 2). For example, the overall rate of infection for dogs on ivermectin, moxidectin SR, or no preventive treatment was 1.03, 1.56, and 3.60 per 1,000 tests, respectively. By contrast, the antigen positive test rate at >9 months following start of the protection period (probably representing treatment failure) for dogs living in a high exposure area for ivermectin, moxidectin SR, and no preventive, were 3.06, 1.98, and 20.52 per 1,000 tests, respectively. The percent protection afforded by ivermectin and moxidectin SR for dogs living in the high exposure states was 85.1% and 90.4%, respectively. The estimated proportion of positive heartworm antigen tests and protection rates for dogs living in the moderate and low risk areas were less stable (wider 95% confidence limits) than in the high exposure area due to the lower number of antigen positive tests in these areas.

The results of multivariable logistic regression analysis (Table 3) generally reflected the observed antigen positive test rates. The risk of a positive antigen test increased in moderate and high risk areas compared with low risk areas, was higher in all age groups compared with dogs <1 year of age, and was higher in all weight groups compared with dogs weighing ≤25 lbs. Males were at significantly increased risk of heartworm infection compared with females while neutered dogs were at significantly decreased risk compared with intact dogs. Mixed breed and pure breed dogs had a similar risk of infection. When dogs were antigen tested at >9 months following a negative antigen test and initiation of heartworm preventive, ivermectin was associated with a 94% reduction in risk of infection (odds ratio = 0.06) and moxidectin SR with a 96% reduction in risk of infection (odds ratio = 0.04) compared with dogs not on

Table 1. Multivariable Logistic Regression Model for the Probability of a Dog Having Been Administered Moxidectin SR Versus Ivermectin at Banfield the Pet Hospital From January 1, 2002 to December 31, 2005.

	Exposure Level		
	High	Moderate	Low
Variable	Odds Ratio (95% CL)		
Gender			
Female	1.00	1.00	1.00
Male	1.02	0.98	0.99
	(0.99 to 1.04)	(0.95 to 1.03)	(0.97 to 1.01)
Neutered			
No	1.00	1.00	1.00
Yes	1.04	1.07	1.14
	(1.02 to 1.07)	(1.03 to 1.12)	(1.11 to 1.17)
Breed			
Pure	1.00	1.00	1.00
Mixed	1.08	1.02	0.98
	(1.05 to 1.11)	(0.97 to 1.09)	(0.95 to 1.02)
Age × Weight Interactions			
<1 year × ≤25 lbs	1.00	1.00	1.00
<1 year × 26-50 lbs	3.14	2.62	2.58
	(3.02 to 3.26)	(2.43 to 2.82)	(2.48 to 2.69)
<1 year × 51-75 lbs	5.31	3.75	3.95
	(5.02 to 5.62)	(3.38 to 4.15)	(3.75 to 4.16)
<1 year × 76-100 lbs	6.43	5.53	4.42
	(5.62 to 7.36)	(4.27 to 7.15)	(3.92 to 4.98)
<1 year × >100 lbs	5.42	5.26	4.77
	(3.82 to 7.70)	(2.92 to 9.47)	(3.49 to 6.52)
≥1 year × ≤25 lbs	8.71	6.90	5.10
	(8.48 to 8.95)	(6.54 to 7.28)	(4.95 to 5.25)
≥1 year × 26-50 lbs	10.33	7.94	6.34
	(10.00 to 10.68)	(7.46 to 8.45)	(6.13 to 6.57)
≥1 year × 51-75 lbs	11.47	9.28	7.67
	(11.09 to 11.86)	(8.72 to 9.88)	(7.41 to 7.93)
≥1 year × 76-100 lbs	12.44	8.90	8.05
	(11.91 to 12.99)	(8.24 to 9.62)	(7.73 to 8.38)
≥1 year × >100 lbs	17.47	12.78	10.64
	(16.13 to 18.92)	(11.20 to 14.58)	(9.92 to 11.41)

CL = confidence limits.

treatment that were tested at <4 months during the protection period.

Residual treatment effectiveness for ivermectin, moxidectin SR, or no preventive treatment was associated with an antigen positive test rate per 1,000 tests of 3.13, 1.68, and 3.33, respectively (Table 4). The decline in effectiveness over time post-treatment was most apparent for dogs living in the high exposure risk areas. For example, residual effectiveness at 1 to 6 months, 7 to 12 months, 13 to 18 months, 19 to 24 months, and 25+ months post-treatment for ivermectin was associated with a rate of 1.65, 7.97, 14.20, 25.97, and 43.81 per 1,000 tests, respectively, while for moxidectin SR rates at corresponding time periods were 3.23, 3.91, 3.39, 4.67, and 5.43, per 1,000 tests, respectively. In fact, the antigen positive test rates with increasing time post-treatment for dogs in the ivermectin group living in the high exposure area were higher at 25+ months post-treatment than for dogs that were not on heartworm preventive and lived in the same risk area (43.81 versus 24.31 per 1,000 tests). The percent residual protection afforded by ivermectin after its use was discontinued, was 86.3% during the first 6 months off treatment, but then declined rapidly to reach only 4.7% by 13 to 18 months post-treatment and 0% by 19 to 24 months (Table 5). In contrast, the residual percent protection afforded by moxidectin SR after its use was discontinued remained at >70% for more than 25 months after cessation of treatment (Table 5).

Table 2. Proportion of Positive Heartworm Antigen Tests per 1,000 Tests for Dogs at Banfield the Pet Hospital from January 1, 2002 to December 31, 2005.

Exposure Level	Month in Protection Period	Ivermectin			Moxidectin SR			No Heartworm Preventive		
		Tested	Positive	% Positive Rats (95% CL)	Tested	Positive	% Positive Rats (95% CL)	Tested	Positive	% Positive Rats (95% CL)
High	1–4	5,720	6	1.05 (0.39 to 2.28)	778	7	9.00 (3.62 to 18.45)	1,573	8	5.09 (2.20 to 10.00)
	5–9	5,001	5	1.00 (0.32 to 2.33)	1,123	4	3.56 (0.97 to 9.09)	2,844	21	7.38 (4.58 to 11.27)
	>9	3,598	11	3.06 (1.53 to 5.46)	8,607	17	1.98 (1.15 to 3.16)	7,992	164	20.52 (17.53 to 23.87)
Moderate	1–4	1,712	0	0.00 (0.00 to 1.75)	340	0	0.00 (0.00 to 8.77)	815	2	2.45 (0.30 to 8.84)
	5–9	1,125	0	0.00 (0.00 to 2.66)	318	1	3.14 (0.08 to 17.40)	1,056	2	1.89 (0.23 to 6.81)
	>9	929	1	1.08 (0.03 to 5.98)	2,330	0	0.00 (0.00 to 1.28)	3,199	17	5.31 (3.10 to 8.49)
Low	1–4	3,792	1	0.26 (0.01 to 1.47)	656	1	1.52 (0.04 to 8.44)	8,873	7	0.79 (0.32 to 1.62)
	5–9	2,467	2	0.81 (0.10 to 2.93)	1,013	1	0.99 (0.02 to 5.49)	14,307	1	0.07 (0.00 to 0.39)
	>9	2,536	1	0.39 (0.01 to 2.20)	6,635	3	0.45 (0.09 to 1.32)	37,780	39	1.03 (0.73 to 1.41)
All	All	26,880	27	1.03 (0.68 to 1.49)	21,802	34	1.56 (1.09 to 2.20)	78,441	261	3.60 (3.18 to 4.06)

All dogs had a negative antigen test within 30 days of being placed on ivermectin or moxidectin SR and were then antigen tested at different months during the protection period.
CL = lower 95% confidence limit to upper 95% confidence limit.

Table 3. Multivariable Logistic Regression Model for the Risk of a Dog Having a Positive Heartworm Antigen Test at Various Times During Heartworm Chemoprophylaxis (treatment effectiveness) at Banfield the Pet Hospital From January 1, 2002 to December 31, 2005.

Variable	Odds Ratio	95% Confidence Limits	*P* Value
Exposure Level			
Low	1.00	NA	NA
Moderate	4.18	2.55 to 6.84	<0.0001
High	16.16	11.90 to 21.95	<0.0001
Age			
<1 year	1.00	NA	NA
1-3 years	10.93	6.30 to 18.96	<0.0001
4-7 years	8.13	4.50 to 14.67	<0.0001
≥8 years	7.20	3.86 to 13.44	<0.0001
Weight			
≤25 lbs	1.00	NA	NA
26-50 lbs	2.51	1.85 to 3.41	<0.0001
51-75 lbs	2.90	2.14 to 3.92	<0.0001
76-100 lbs	2.36	1.56 to 3.58	<0.0001
>100 lbs	2.81	1.51 to 5.22	0.0010
Breed			
Pure	1.00	NA	NA
Mixed	1.07	0.75 to 1.51	0.6982
Gender			
Female	1.00	NA	NA
Male	1.31	1.04 to 1.65	0.0220
Neuter			
No	1.00	NA	NA
Yes	0.31	0.25 to 0.40	<0.0001
Treatment × Months' Protection Interactions			
No treatment × 1-4 months	1.00	NA	NA
No treatment × 5-9 months	0.52	0.27 to 1.01	0.0517
No treatment × >9 months	0.35	0.19 to 0.62	0.0004
Ivermectin × 1-4 months' protection	0.25	0.10 to 0.64	0.0036
Ivermectin × 5-9 months' protection	0.20	0.08 to 0.49	0.0005
Ivermectin × >9 months' protection	0.06	0.02 to 0.14	<0.0001
Moxidectin SR × 1-4 months' protection	0.70	0.29 to 1.68	0.4284
Moxidectin SR × 5-9 months' protection	0.13	0.05 to 0.36	<0.0001
Moxidectin SR × >9 months' protection	0.04	0.02 to 0.08	<0.0001

All dogs had a negative antigen test within 30 days of being placed on ivermectin or moxidectin SR and were then antigen tested at different months during the protection period.

Multivariable logistic regression analysis (Table 6) as expected showed that the risk of heartworm infection increased following cessation of heartworm preventive treatment for dogs living in the highest exposure areas; these dogs had a risk of heartworm infection almost 19-times higher (odds ratio = 18.47) than for dogs living in the lowest exposure areas. The highest risk of infection was for dogs age 1 to 3 years old and in each weight category for dogs weighing >25 lbs the risk was significantly elevated. The residual treatment effectiveness was not significantly increased for mixed breed versus pure breed dogs, but males had a significantly increased risk compared with females. The risk of infection of neutered dogs was 65% less (odds ratio = 0.35) than for intact dogs. These risk patterns may reflect a dog's outdoor activity.

The risk of heartworm infection for dogs that had been on ivermectin but then stopped taking the heartworm preventive increased steadily over time since treatment (Table 6). For example, their risk of infection during the first 6 months and second 6 months post-treatment was 77% (odds ratio = 0.23) and 23% (odds ratio = 0.77) lower, respectively, compared with dogs that were not on treatment during the first 6 months of observation. After 12 months post-treatment, however, the risk of infection for the dogs that had been on ivermectin increased and was almost 300% higher (odds ratio = 3.60) at 25+ months post-protection. In contrast, the risk of heartworm infection for dogs that had been on moxidectin SR remained significantly lower for up to 2 years post-treatment compared with dogs that were not on treatment during the first 6 months of observation and was still approximately 60% lower (odds ratio = 0.41) even at 25+ months post-treatment. Overall, the risk of heartworm infection increased significantly ($P < 0.0001$, linear test for trend) over time following treatment with ivermectin, while the risk remained constant and consistently low ($P = 0.85$, linear test for trend) following moxidectin treatment.

DISCUSSION

Chemoprophylaxis is recognized as the most effective method to prevent heartworm infection in dogs. Ivermectin, when administered at prescribed doses at monthly intervals, is virtually 100% effective. An additional month of protection is afforded in the event owners miss administration of a dose. This is an important feature of the macrocyclic lactones, since owner lack of compliance with instructions for monthly administration occurs frequently and is believed to be the most common explanation for treatment failures when dogs are on a regimen of oral monthly heartworm prevention.[6] In contrast, moxidectin SR, when administered subcutaneously at the prescribed dose, confers 100% protection against challenge inoculation with *D. immitis* for at least 180 days,[3] but the length of protection afforded if an owner decides not to continue treatment with moxidectin SR was not previously known. The evaluation of the effectiveness of heartworm chemoprophylaxis has been primarily based on experimental studies in laboratory dogs rather than post-marketing field studies.

Recent reports of heartworm chemoprophylaxis failure to the FDA CVM and directly to manufacturers[7] indicates that owner compliance with oral administration of heartworm chemoprophylaxis is a significant problem and was pronounced after ProHeart 6 was withdrawn from the market. The FDA CVM suggested that this lack of effectiveness for orally administered chemoprophylaxis probably reflects some combination of drug failure, lack of owner compliance with administration of oral products, and reporting biases of pet owners and veterinarians. In contrast, the study reported here using the electronic medical records of a nationwide veterinary practice was unaffected by reporting bias since determination of drug failure was based solely on results of antigen tests recorded in each dog's medical record. In addition, this study was conducted for a time period during which both oral ivermectin and parenteral moxidectin SR were still on the market and being used by Banfield veterinarians. These study results, therefore, should not have been biased in terms of which dogs received oral versus parenteral heartworm chemoprophylaxis, except that ivermectin was the preferred choice for

Table 4. Proportion of positive Heartworm Antigen Tests per 1,000 Tests During Different Times (post protection months) After a Dog Stopped Taking Heartworm Prophylaxis at Banfield the Pet Hospital From January 1, 2002 to December 31, 2005.

Exposure Level	Month in Protection Period	Ivermectin			Moxidectin SR			No Heartworm Preventive		
		Tested	Positive	% Positive Rats (95% CL)	Tested	Positive	% Positive Rats (95% CL)	Tested	Positive	% Positive Rats (95% CL)
High	1–6	14,563	24	1.65 (1.06 to 2.45)	18,887	61	3.23 (2.47 to 4.15)	4,639	56	12.07 (9.13 to 15.65)
	7–12	5,521	44	7.97 (5.80 to 10.68)	10,491	41	3.91 (2.81 to 5.30)	2,866	60	20.94 (16.01 to 26.87)
	13–18	1,620	23	14.20 (9.02 to 21.23)	2,946	10	3.39 (1.63 to 6.23)	1,409	21	14.90 (9.25 to 22.69)
	19–24	847	22	25.97 (16.35 to 39.06)	1,284	6	4.67 (1.72 to 10.14)	928	15	16.16 (9.07 to 26.52)
	25+	525	23	43.81 (27.97 to 65.01)	736	4	5.43 (1.48 to 13.88)	864	21	24.31 (15.11 to 36.91)
Moderate	1–6	3,828	0	0.00 (0.00 to 0.78)	5,372	8	1.49 (0.64 to 2.93)	1,884	4	2.12 (0.58 to 5.43)
	7–12	1,672	6	3.59 (1.32 to 7.79)	2,920	5	1.71 (0.56 to 3.99)	1,132	7	6.18 (2.49 to 12.70)
	13–18	504	1	1.98 (0.05 to 11.00)	786	1	1.27 (0.03 to 7.07)	604	7	11.59 (4.67 to 2.3.73)
	19–24	331	1	3.02 (0.08 to 16.72)	348	1	2.87 (0.07 to 15.91)	482	0	0.00 (0.00 to 6.46)
	25+	247	1	4.05 (0.10 to 22.35)	215	0	0.00 (0.00 to 13.84)	402	1	2.49 (0.06 to 13.78)

Exposure Level	Month in Protection Period	Ivermectin			Moxidectin SR			No Heartworm Preventive		
		Tested	Positive	% Positive Rats (95% CL)	Tested	Positive	% Positive Rats (95% CL)	Tested	Positive	% Positive Rats (95% CL)
Low	1–6	11,929	5	0.42 (0.14 to 0.98)	23,778	10	0.42 (0.20 to 0.77)	20,427	10	0.49 (0.23 to 0.90)
	7–12	5,380	6	1.12 (0.41 to 2.43)	13,414	1	0.07 (0.00 to 0.42)	15,039	13	0.86 (0.46 to 1.48)
	13–18	1,745	0	0.00 (0.00 to 1.72)	3,636	0	0.00 (0.00 to 0.82)	7,378	5	0.68 (0.22 to 1.58)
	19-24	998	2	2.00 (0.24 to 7.22)	2,024	0	0.00 (0.00 to 1.48)	5,830	8	1.37 (0.59 to 2.70)
	25+	822	0	0.00 (0.00 to 3.64)	1,130	0	0.00 (0.00 to 2.65)	5,531	3	0.54 (0.11 to 1.58)
All	All	50,532	158	3.13 (2.94 to 4.03)	87,967	148	1.68 (1.62 to 2.11)	69,395	231	3.33 (3.54 to 4.99)

The incidence rates reflect residual treatment effectiveness of heartworm chemoprophylaxis. All dogs had a negative antigen test within 30 days of being placed on ivermectin or moxidectin SR and were then antigen tested at different months during the post-protection period.
CL = lower 95% confidence interval to upper 95% confidence interval.

dogs <6 months of age and moxidectin SR the preferred choice for dogs ≥6 months of age.

The study showed that the effectiveness of both orally administered ivermectin and parenterally administered moxidectin SR were high, but less than 100%. For example, using American Heartworm Society[2] criteria for drug failure, ivermectin and moxidectin SR were 94% and 96% effective, respectively, during the period of expected label protection. The less-than-perfect protection afforded by both ivermectin and moxidectin SR confirmed that experimental challenge studies in small numbers of laboratory dogs and limited field trials conducted by veterinary practitioners on client-owned pets does not mirror performance of drugs post-marketing. Effectiveness of drugs administered to pet dogs by owners and veterinarians is probably affected by a number of factors including inter-individual (both dog and owner) variability, the health status of the dog at the time of administration, the age of the dog, genetics or physiology, concurrent administration of other drugs and vaccines, diet, stress, a dog's level of outdoor activity, and other yet unidentified factors.

The length of heartworm transmission is highly dependent on environmental temperatures, since sufficient heat is needed to incu-

Table 5. Effectiveness of Ivermectin and Moxidectin SR to Prevent Heartworm Infection at Different Time Periods After Chemoprophylaxis Was Discontinued.

Month After Protection Period Ends	Ivermectin % Protection*	Moxidectin SR % Protection*
1-6	86.3	73.2
7-12	61.9	81.3
13-18	4.7	77.2
19-24	0.0	71.1
25+	0.0	77.7

*Compared with dogs on no heartworm preventive.

bate larvae to the infective stage in the mosquito. The peak months of mosquito transmission are typically July and August. The period of *D. immitis* transmission is estimated to range from less than 4 months in southern Canada to potentially all year round in parts of southern Florida and the Gulf Coast.[2] Given this wide variability in exposure of dogs to infected mosquitoes, recommendations for heartworm chemoprophylaxis vary by location. Continuous year-round heartworm chemoprophylaxis is preferable in regions where transmission might occur more than half the year, especially when using monthly treatments since compliance is known to be a serious problem throughout the country.[2] In order to overcome lack of compliance by owners, chemoprophylactic agents with extended activity are beneficial and these may also help reduce the risk of zoonotic dirofilariasis.[8]

Although neither orally administered ivermectin products or injectable moxidectin SR has a label claim for residual heartworm prophylactic activity, one of the objectives of the present study was to estimate the length of residual treatment effectiveness for ivermectin and moxidectin SR under field conditions. The results of this study showed that ivermectin was partially protective against heartworm infection in dogs for up to 1 year post-treatment, but it provided little or no protection beyond 1 year. In contrast, moxidectin SR at the recommended dose provided at least 70% protection for more than 2 years. This suggests that sustained-release moxidectin protects for a longer period than suggested previously and is the preferred method for extended, residual protection in heartworm endemic areas and whenever owner compliance is a concern. When interpreting residual treatment effectiveness, it is important to consider that the pre-patent period for *D. immitis* in dogs is approximately 6 months[9] and that antigen tests are not positive before 5 months after infection.[10] Also, the apparent residual effectiveness associated with ivermectin may be due to owners administering doses of ivermectin well after the date on which it was originally obtained from the veterinarian.

The risk of heartworm infection was higher 24 months post-treatment for dogs that lived in high exposure areas and had received ivermectin than it was for dogs that had not received heartworm preventive (Table 4). For example, the infection rate for ivermectin compared to no heartworm treatment was 43.81 versus 24.31 antigen positive tests per 1,000 dogs tested. These findings are similar to a study in which cattle living in Africa where *Ochocerca volvulus* transmission is high were treated with either moxidectin SR or ivermectin for almost 2 years. When all drug treatments were withdrawn and a non-treated control group was introduced, the cattle in the ivermectin group were found to be hypersusceptible to infection.[11] In addition, microfilarial densities and the rate of increase in microfilaria load were significantly higher in the ivermectin-treated group, but not in the moxidectin-treated group, compared with the control animals. These results indicating significantly greater susceptibility to infection among cattle that had received ivermectin treatment, but were then removed from treatment, has serious implications in the context of mass drug treatment programs currently enacted globally that utilize ivermectin against human onchocerciasis,[12] but not for possible future programs that would be based on moxidectin treatment. Similar hypersusceptibility to *D. immitis* infection in dogs following cessation of

Table 6. Multivariable Logistic Regression Model for the Risk of a Dog Having a Positive Heartworm Antigen Test at Various Times After Heartworm Chemoprophylaxis (residual treatment effectiveness) at Banfield the Pet Hospital From January 1, 2002 to December 31, 2005.

Variable	Odds Ratio	95% Confidence Limits	*P* Value
Exposure Level			
Low	1.00	NA	NA
Moderate	5.49	3.69 to 8.16	<0.0001
High	18.47	13.93 to 24.50	<0.0001
Age			
<1 year	1.00	NA	NA
1-3 years	2.75	1.55 to 4.88	0.0005
4-7 years	1.71	0.94 to 3.11	0.0771
≥8 years	1.35	0.72 to 2.52	0.3465
Weight			
≤25 lbs	1.00	NA	NA
26-50 lbs	2.08	1.64 to 2.64	<0.0001
51-75 lbs	2.65	2.10 to 3.33	<0.0001
76-100 lbs	2.64	1.93 to 3.60	<0.0001
>100 lbs	3.17	1.97 to 5.10	<0.0001
Breed			
Pure	1.00	NA	NA
Mixed	1.18	0.92 to 1.53	0.1879
Gender			
Female	1.00	NA	NA
Male	1.22	1.02 to 1.46	0.0253
Neuter			
No	1.00	NA	NA
Yes	0.35	0.29 to 0.42	<0.0001
Treatment × Months' Protection Interactions			
No treatment × 1-6 months	1.00	NA	NA
No treatment × 7-12 months	1.68	1.21 to 2.35	0.0020
No treatment × 13-18 months	1.55	1.02 to 2.38	0.0399
No treatment × 19-24 months	1.63	1.01 to 2.64	0.0459
No treatment × 25+ months	2.01	1.25 to 3.23	0.0036
Ivermectin × 1-6 months' protection	0.23	0.14 to 0.37	<0.0001
Ivermectin × 7-12 months' protection	0.77	0.53 to 1.11	0.1627
Ivermectin × 13-18 months' protection	1.17	0.73 to 1.89	0.5048
Ivermectin × 19-24 months' protection	2.44	1.53 to 3.91	0.0002
Ivermectin × 25+ months' protection	3.60	2.22 to 5.82	<0.0001
Moxidectin SR × 1-6 months' protection	0.28	0.20 to 0.39	<0.0001
Moxidectin SR × 7-12 months' protection	0.29	0.20 to 0.42	<0.0001
Moxidectin SR × 13-18 months' protection	0.28	0.15 to 0.52	<0.0001
Moxidectin SR × 19-24 months' protection	0.40	0.18 to 0.89	0.0251
Moxidectin SR × 25+ months' protection	0.41	0.15 to 1.15	0.0911

All dogs had a negative antigen test within 30 days of being placed on ivermectin or moxidectin SR and were then antigen tested at different months during the post-protection period.

ivermectin use could be a serious problem in areas of the country where ivermectin is used during only part of the year for heartworm prevention in dogs or when owners fail to continue year-round monthly administration of ivermectin in endemic heartworm areas. For this reason, this phenomenon deserves further study.

CONCLUSION

This nationwide, post-marketing, epidemiological study using >11 million electronic medical records for dogs visiting >500 Banfield veterinary hospitals indicates that both ivermectin and moxidectin SR are highly effective for the prevention of heartworm infection in dogs, but as expected, the 100% efficacy reported for both drugs in limited pre-clinical laboratory studies with experimentally induced infections and field trials with client-owned dogs, was not attained. However, once chemoprophylaxis is discontinued, the residual effectiveness of moxidectin SR lasts significantly longer than for ivermectin. The results of this study, as well as a similar study on the safety of heartworm preventives in dogs, illustrate the value of using nationwide veterinary practices for post-marketing surveillance of veterinary drugs.[5] Pharmacoepidemiological studies like these will become more common as veterinary practices become computerized and standardize their medical record-keeping systems. Epidemiological studies are not meant to replace laboratory studies, but rather to evaluate the safety and effectiveness of drugs under field conditions. No drug is ever completely effective or safe. The results of post-marketing studies can help veterinarians perform a quantitative risk assessment for individual patients in order to choose the most appropriate treatment or prevention strategy. The practice of evidence-based veterinary medicine is dependent on the availability of well-controlled studies performed under conditions similar to those for patients for whom clinical decisions are to be made.

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