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Preventive Veterinary Medicine 72 (2005) 311–322

PREVENTIVE VETERINARY MEDICINE

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The effective life of ivermectin on Western Australian sheep farms—A survival analysis

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Received 7 May 2004; received in revised form 28 July 2005; accepted 28 July 2005

Abstract

A mail survey of 235 Western Australian sheep farmers who had performed faecal egg count reduction tests for anthelmintic resistance in 1999 or 2000 was conducted, with some telephone follow-up. A response of 56% was achieved. Resistance to ivermectin, a member of the macrocyclic lactone class of anthelmintics, had developed on 44% of the farms surveyed. We used time to occurrence of resistance to ascertain factors that contributed to extending the time ivermectin remained an effective drench on these farms (median time = 10.5 years). This time was significantly longer when farmers implemented more worm control practices on their farms ($P = 0.003$). We developed a multivariable survival model that contained the following main effects: reduced winter drenching frequency, 0–2 flock treatments in 5 years (hazard ratio (HR) 0.52); availability of alternative effective anthelmintic classes on the farm (HR 0.30); always using safe pastures (HR 0.23); and veterinarians as the primary source of worm control advice (HR 0.58). The relationship of these findings to the understanding of anthelmintic resistance is discussed.

Keywords: Ivermectin; Anthelmintic resistance; Sheep; Survival analysis; Farm management; *Ostertagia circumcincta*

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doi:10.1016/j.prevetmed.2005.07.014

1. Introduction

Gastrointestinal parasitism is widely regarded as the major disease problem of sheep in Australia (Love and Coles, 2002). Nematodes from three genera are recognised as being the most pathogenic, causing the majority of production losses: *Haemonchus contortus*, *Ostertagia* (*Teladorsagia*) *circumcincta* and *Trichostrongylus* spp. The latter two predominate in Western Australia (WA), which has a Mediterranean environment with winter rainfall. The prevalence of ivermectin resistance in *O. circumcincta* in Western Australia has risen rapidly, whereas it is uncommon in other regions of Australia (Besier and Love, 2003). Palmer et al. (2001) estimated the farm level prevalence of macrocyclic lactone (ML) resistance in WA to be 44%, based on faecal egg count reduction test (FECRT) results where less than a 95% reduction was achieved after treatment with a half dose of ivermectin. Ivermectin resistance was confirmed on half of those properties. As yet ivermectin resistance in *Trichostrongylus* species is unreported in Australia, but it is becoming prevalent in *H. contortus* in those areas where this species is endemic (Love and Coles, 2002).

Ivermectin is a member of the ML class of anthelmintics that includes moxidectin and abamectin. Although cross-resistance between members of this class has been demonstrated to occur, resistance occurred first to ivermectin because it has been available for the longest and is the least potent of the MLs against *O. circumcincta* (Leathwick et al., 2000). The class is the most recent of the modern anthelmintics available to sheep producers (Geary et al., 1999), and it is anticipated that resistance to this class will pose a serious problem for farmers as the prevalence of resistance to the older anthelmintic classes, the benzimidazoles and imidazothiazoles, is already over 80% in Australia (Overend et al., 1994). A review by Prichard et al. (1980) listed the prevailing hypotheses concerning the development of anthelmintic resistance as over-drenching, under-dosing, lack of *refugia* (where part of the parasite population is not exposed to anthelmintic treatment) and reversion to susceptibility. Recommendations from this review have been actively promoted by Australian State Departments of Agriculture in extension programs (Waller et al., 1995). These programs have become accepted as best-practice parasite management programs followed worldwide in all animal species (Geerts and Gryseels, 2001). The programs recommend routine testing for anthelmintic resistance, using strategic treatments (anthelmintic treatment at critical times in the parasite life cycle) and safe pastures after drenching, minimising anthelmintic use, routine laboratory monitoring for parasitism, annual rotation between effective chemicals, and quarantine drenching of introduced stock to prevent the incursion of resistant parasites. The rapid rate at which ivermectin resistance has risen has led to a reappraisal of these programs. In particular, in light of the "*refugia*" hypothesis (Prichard et al., 1980; van Wyk, 2001), it has been proposed that the effectiveness of the strategic "summer drenching program" in controlling these parasites in winter rainfall regions may actually contribute to the high prevalence of resistance (Besier, 1997). The *refugia* hypothesis states that lack of *refugia* leads to a situation where the source of the future worm population is derived chiefly from those resistant to prior treatment. In WA there is little *refugia* for the worms on a farm when all sheep are treated with anthelmintic in summer, because virtually no worm larvae survive on pasture. It has also been proposed that anthelmintic resistance may increase in a similar

manner when sheep are drenched and moved to a "safe" pasture, which has low levels of infective larvae (van Wyk, 2001). There have been few epidemiological studies of anthelmintic resistance at the farm level (Coles, 2002). In a companion study to this, Suter et al., (2004) produced a main effects logistic regression risk factor model for ivermectin resistance on Western Australian sheep farms, from the results of a postal questionnaire sent to farmers who had conducted anthelmintic resistance testing in 1999–2000. The main effects found to correlate with occurrence of resistance were winter anthelmintic treatment frequency, excess sheep sales and duration of farm ownership. In this paper, we present a survival model derived from the same data set, enhanced by follow-up telephone interviews with the respondent farmers. This analysis extends the previous study by examining the rate of development of resistance, thus enabling identification of those factors that contributed to extending the length of time that ivermectin remained an effective drench. In particular, we further explore the influence of farm management practices.

2. Methods

A postal survey was sent to all 235 farmers in WA known to have conducted an anthelmintic-resistance test (FECRT) (Lyndall-Murphy, 1993) in sheep in either 1999 or 2000 (or both). The questionnaire contained 53 questions including descriptors of the farm and its enterprises, and questions addressing hypotheses concerning the development of anthelmintic resistance. For example, questions on summer drenching, the use of safe pastures, and environmental influences (longer, dryer summers) were included to examine aspects of the *refugia* hypothesis. Other questions enabled investigation of the effects of flock anthelmintic treatment frequency, underdosing, use of quarantine drenching, sheep trading, and the influence of the farmer's management skill upon the risk of developing ivermectin resistance. Thirty-two of the questions in the questionnaire were open-ended. The questionnaire was pilot tested by five farmers who were not surveyed, although repeatability of answers was not tested directly. The questionnaire took 2–4 h to complete.

Telephone follow-up was conducted with 38 of the respondent farmers in 2002 to determine the year in which they had first used ivermectin on their sheep, as they had not answered this question when returning the questionnaire. When applicable these farmers also provided the results of any FECRT conducted since 2000.

Results of the FECRTs had been collated by the Department of Agriculture, Western Australia. The standard FECRT has treatment groups dosed with the recommended label dose of anthelmintic. Some of these tests also included a half dose ivermectin group as suggested by Palmer et al. (2001), to provide better discrimination between farms for ML resistant *Ostertagia*. Farms were defined as either ivermectin-resistant or not ivermectin resistant. Resistant farms were those with a <95% reduction in a FECRT by one or more of three criteria:

- overall reduction of strongyloid eggs,
- reduction of *Ostertagia* only, or
- reduction of *Ostertagia* after a half dose of ivermectin.

The farm-level prevalence of ivermectin resistance amongst respondents and non-respondents was calculated, and independence assessed with a Chi-square test.

The effective life of ivermectin on a farm was defined as the time (in years) from first use of ivermectin until the occurrence of ivermectin resistance. The time to resistance on those farms not yet diagnosed as such when surveyed were right censored at the time of their last FECRT. For those farms found to be resistant the times at which this occurred were interval censored in that they were known to fall in the interval between the last negative and the first positive tests but were not known exactly. The mid-points of these intervals were used as approximations to the true times for construction of Kaplan–Meier survival plots, obtaining summary statistics and Cox regression modelling. Similar results were obtained by incorporating the end-points of the intervals in an approach based on maximum-likelihood estimation of a Weibull distribution (results not shown).

The effects of various farm level risk factors on the effective life of ivermectin were modelled under an assumption of proportional hazards within the Cox regression framework, with standard two-sided Wald tests used for assessment of the effects. Two approaches were used. Firstly worm management intensity was assessed by construction of a score based on the number of best-practice strategies adopted on respondent farms. Secondly a multivariable survival model was developed to ascertain those factors with most influence on development of resistance. Variables with $P < 0.15$ in univariable analyses were included for consideration in this model and a backwards-stepwise elimination approach was used for its development, with a threshold P-value of 0.10 for retention of variables. The suitability of the proportional hazards assumption was checked by application of the test of Grambsch and Therneau (1994) prior to removal of any variable. Where appropriate, aggregation of categorical variables was undertaken based upon a priori assumptions. Some continuous variables, such as the number of winter drenches in 5 years, were recoded into categorical variables with the demarcation being the median value. The multivariable model was checked for interactions amongst the main effects variables within the model.

Analyses were performed using S-Plus (2002, Version 6).

3. Results

A response of 56% was achieved (132 from 235). The prevalence of ivermectin resistance amongst respondents was 44%. Respondents were no more likely than non-respondents to have ivermectin resistance on their farm ($P = 0.55$). On average respondents had conducted 3.5 drench resistance tests (range 1–15) at a mean interval of 3.8 years (range 1–13, standard deviation 3.2). Replies were excluded from all analyses if time of first use could not be ascertained or ivermectin had never been used as a sheep anthelmintic on the farm. Further exclusion occurred when relevant covariate values were missing. In total, 108 farms were included in the final models, and those farms had a period prevalence of ivermectin resistance of 48% (95% CI 39%, 58%). From the Kaplan–Meier survival curve of Fig. 1, the estimated median time to development of resistance amongst respondent farmers was 10.5 years. Farmers were assigned a worm management score according to a count of the following indicators of management skill and best-practice

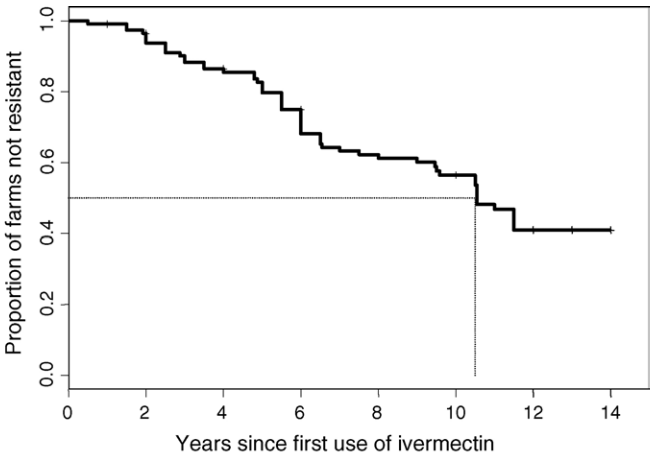

Fig. 1. Kaplan–Meier survival plot for the effective life of ivermectin on Western Australian sheep farms (data to 2001).

strategies adopted: frequent users of laboratory monitoring (perform FECRT annually, and > 3 faecal worm egg counts each year), early first summer drenching (before December), consistent use of safe pastures after drenching, use of quarantine drenching, annual rotation of drench classes, availability of an effective alternative anthelmintic class, consistent calibration of the drench gun, no more than two annual summer treatments and no more than two winter flock treatments over 5 years. Fig. 2 displays Kaplan–Meier survival plots of time to development of ivermectin resistance stratified by the worm management score. A higher score was associated with longer time to occurrence of resistance ($P = 0.003$).

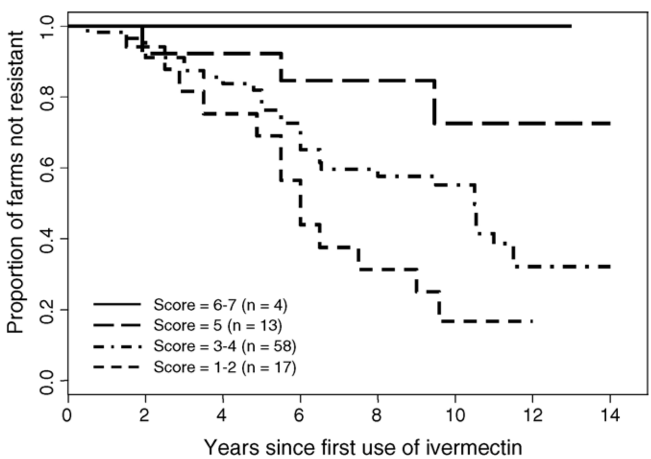

Fig. 2. Kaplan–Meier survival plots for the effective life of ivermectin, stratified by worm management score, on Western Australian sheep farms (data to 2001).

Table 1
Cumulative survival times for the effective life of ivermectin from a survey of Western Australian sheep farmers (data to 2001)

Variable	Level	*n*	Quartiles of cumulative survival (years)		
			75%	50%	25%
1. Type of sheep enterprise[a]	All wool sheep	43	4.8	9.5	–
	Some prime lambs	66	6.0	–	–
2. Wool micron	18.5–20.0	35	5.5	10.5	–
	20.1–20.5	21	5.0	10.5	–
	20.6–21.4	26	6.0	10.5	10.5
	21.5–30.0	28	9.6	–	–
3. Does the farm have crop[a]	No	11	6.0	7.0	10.5
	Yes	104	5.5	11.5	–
4. Does the farm graze cattle[a]	No	32	6.0	10.5	–
	Yes	83	5.5	–	–
5. Worm Control Zone (farm environment)	Coastal, high rainfall	95	6.0	11	–
	Inland, drier	20	4.9	6.5	–
6. Frequent laboratory monitoring[b]	No	98	5.5	10.5	
	Yes	5	9.5	10.5	11.5
7. Timing of first summer drench[b]	October–November	17	5.5	10.5	–
	December	63	6.0	10.5	–
	January–March	30	5.5	–	–
8. Number of summer drenches[b]	0–1	80	5.5	10.5	–
	2	27	6.0	10.5	–
	3–4	8	6.0	10.5	11.5
9. Always uses safe pastures after drenching[a,b]	No	89	5.5	9.5	–
	Yes	23	–	–	–
10. Used macrocyclic lactone quarantine drenches in 2000	No	60	5.5	10.5	–
	Yes	55	6.0	10.5	–
11. Used quarantine drenches in 1995[b]	No	76	5.5	10.5	–
	Yes	49	6.5	–	–
12. Used ivermectin in 1995 for quarantine drenching	No	70	5.5	11.0	–
	Yes	44	6.0	10.5	–
13. Length of farm ownership[a]	25 years+	58	5.0	9.0	–
	<25	54	6.5	11.0	–
14. Main source of worm control advice used on the farm[a]	Government veterinarian	39	6.0	11.0	–
	Private veterinarian	8	7.5	–	–
	Consultant	54	5.0	10.5	–
	Other	13	3.5	6.5	–
15. Annual rotation of drench classes[a,b]	No	70	6.5	9.5	–
	Yes	45	5.0	–	11.5

Table 1 (*Continued*)

Variable	Level	*n*	Quartiles of cumulative survival (years)		
			75%	50%	25%
16. Number of alternative anthelmintic classes[a,b]	0	85	5.5	9.5	–
	1	18	–	–	–
	2	8	10.5	11.5	11.5
17. Calibrate the drench gun[b]	No	6	4.8	4.9	–
	Yes	107	6.0	10.5	–
18. Sheep sales in 2000[a]	The same or less	83	6	11.5	–
	More than usual	30	5	9.6	11.5
19. Number of winter flock treatments 1996–2000[a,b]	0	38	7.0	–	–
	1–2	27	6.0	11.0	–
	3–5	25	3.5	6.0	–
	6–66	25	6.0	9.6	11.5
20. Aggregated no. winter flock treatments 1996–2000[a]	0–2	65	6.5	–	–
	3–66	50	4.9	9.5	–
21. No. winter flock treatments with moxidectin 1996–2000[a]	0	94	6.0	–	–
	1–4	21	2.5	6.5	10.5
22. No. winter flock treatments with macrocyclic lactones 1996–2000[a]	0	64	6.0	–	–
	1–2	28	5.5	8.0	–
	3–8	23	5.0	9.5	11.5
23. Annual anthelmintic use (average winter treatments plus summer drenches)[a]	0–1	30	7.0	–	–
	1.1–1.8	28	5.5	10.5	–
	1.9–2.7	28	5.5	–	–
	2.8–14.2	29	5.5	9.5	11.5

Estimates were obtained from unadjusted Kaplan–Meier plots; continuous variables were stratified into intervals determined by their quartile values. (–) Covariate did not attain the quartile in Kaplan–Meier.

[a] Variable offered to the multivariable model.

[b] Variable contributed to worm management score.

The variables tested in the univariable analyses to develop the main effects multivariable model are presented in Table 1. Fourteen variables were offered to the multivariable model. These variables reflected farm enterprise type (variables 1, 3, and 4), the *refugia* hypothesis (variable 9), the drenching frequency hypothesis (variables 19–23), sheep trading practices (variables 13 and 18), the number of effective anthelmintic groups (variables 15 and 16), and the primary source of worm control advice (variable 14). The stepwise selection process that jointly considered these variables yielded a model with four main effects for the effective life of ivermectin on WA sheep farms. These effects were reduced winter drenching frequency (0–2 flock treatments in 5 years), availability of alternative effective anthelmintic classes on the farm, always using safe pastures and veterinarians as the primary source of worm control advice.

The estimated, adjusted hazard ratios of the four variables remaining as covariates in the final model are provided in Table 2. The hazard ratios give the relative probabilities of developing resistance at any particular time, given survival up to that time and with the

Table 2
Multivariable Cox model for the effective life of ivermectin on 108 Western Australian sheep farms (data to 2001)

Variable	Covariate	*P*	HR	95% CI
Number of winter flock treatments in 5 years	0–2	0.03	0.53	0.30, 0.94
	3–66		1	
Use of safe pastures after drenching	Always	0.01	0.22	0.07, 0.73
	Less frequently		1	
Effective alternate anthelmintics available	Yes	0.01	0.30	0.12, 0.77
	No		1	
Main source of worm control advice	Veterinarians	0.09	0.60	0.33, 1.08
	Other		1	

other covariate values taking fixed values. There were no significant interactions between the variables of the final model, implying the effects are additive.

4. Discussion

The majority of epidemiological studies on anthelmintic resistance have been surveys to determine prevalence at a particular time point (reviewed by Prichard, 1990; Coles, 2001; Barger, 2002; Sangster and Dobson, 2002). Studies that have examined risk factors for resistance at a particular point in time include those by Edwards et al. (1986), Bartley et al. (2003), Ancheta et al. (2004), and Suter et al. (2004). This is the first study to examine the rate at which anthelmintic resistance develops by producing a survival model for the effective life of ivermectin on WA sheep farms.

The study of Suter et al. (2004) suggested that farmer commitment to worm control strategies reduces risk of ivermectin resistance. To further explore this observation we devised a score based on the number of strategies advocated as best-practice which had been adopted by the respondent farmers. The survival plots of Fig. 2 show that the effective life of ivermectin was prolonged on those farms that scored more highly. In particular, farms where less than three of these were employed had a median survival time about half that of the median of the whole cohort studied, whilst ivermectin resistance had not developed on any of those where at least six of these strategies had been employed. This suggests it may be beneficial to implement a suite of strategies to control a multi-factorial problem such as anthelmintic resistance, although many farmers appear to have some difficulty in doing this. This finding supports the approach that has been promoted in State Government extension campaigns to control anthelmintic resistance.

A multivariable model was developed to identify those variables of most influence on the effective life of ivermectin. Of note all variables remaining in the final model related to management practices incorporated in the worm management score rather than environmental and enterprise variables.

It was found that farms on which less than three winter drenches were given every 5 years developed ivermectin resistance at a rate about half that of farms where more frequent winter drenching was practised. The significance of a variable relating to winter

drench use supports the drenching frequency hypothesis proposed by Prichard et al. (1980), which states that frequent drenching increases the rate of selection, by increasing selection pressure. Some authors believe that drenching frequency was the main factor in the development of benzimidazole and imidazothiazole (i.e., levamisole) resistance in all genera, and in ML resistance in *H. contortus* (Besier and Love, 2003). It has been proposed that the *refugia* hypothesis is more likely than the drenching frequency hypothesis to explain the development of ivermectin resistance in *Ostertagia drcumcincta* in WA, as a consequence of the routine practice of summer drenching (Besier, 1999). In this study, all respondent farms practised summer drenching; further winter drenching would provide additional selection pressure to that imposed by the summer drenches.

In a survey of anthelmintic resistance in the early 1990s it was estimated that 80% of WA farms had resistance to the imidazothiazole class of anthelmintics and 88% to the benzimidazole class (Overend et al., 1994). Prichard et al. (1980) proposed that anthelmintics should be rotated between classes to prolong the effective life of each of the anthelmintics. This rotation of anthelmintics was believed to allow reversion to effectiveness of an anthelmintic to which resistance had been developing (Prichard et al., 1980). However, field experiments to confirm the rotation hypothesis have been equivocal (Leathwick et al., 2001), and reversion has not been shown to occur in practice (van Wyk, 2001). The survival model presented here found that availability of an alternative anthelmintic class on the farm was significantly associated with a reduced rate of development of ivermectin resistance (HR = 0.3), whereas adoption of the practice of annual rotation did not significantly add to the model.

A ‘‘safe pasture’’ is a pasture carrying very low levels of infective nematode larvae, so that sheep moved to safe pastures after drenching do not rapidly become re-infected. These pastures can be prepared in a number of ways including prior grazing by adult dry sheep that are not producing significant numbers of nematode eggs, grazing by cattle (Barger and Southcott, 1978), or by other agricultural use such as cropping and haymaking. The time required to produce a safe pasture by these methods depends upon seasonally variable effects on the survival of worm nematode larvae, and in WA is estimated to be 1–3 months during summer and 6 months during winter. Thus, farmers need to plan sheep grazing movements to ensure that safe pastures will be available when flocks need treating. Whilst the use of safe pastures for grazing sheep after anthelmintic treatment has been promoted as a method of worm control it has also been suggested that it is another instance of a strategic treatment which, like summer drenching, could promote anthelmintic resistance under the *refugia* hypothesis (van Wyk, 2001). Counter to this supposition, however, we found the practice was associated with a protective hazard ratio, both in the univariable and the multivariable models. Whilst this somewhat surprising result may be explained by the inability of this investigation to capture the possibility that sufficient *refugia* were provided elsewhere on the farms, from these findings it would appear that overall the benefits of consistently using safe pastures after drenching outweigh the risks.

The last variable in the model for the effective life of ivermectin was the source of worm control advice utilised by the farmer. Farmers who used veterinarians as their primary source of worm control advice were about half as likely to develop ivermectin resistance each year as farmers who relied upon other sources of advice on managing worm control.

The covariate ‘‘Veterinarians as primary source of worm control advice’’ included both private veterinarians and government veterinary officers; the other sources of advice included farm consultants, neighbouring farmers, farm magazines, and radio broadcasts. Respondents using veterinarians for advice were considered indicative of farmers that were committed to sourcing the most up-to-date scientific advice for managing worm control for their sheep enterprise.

The findings of this study are based on results of FECRT, which despite limitations, is recognised as the most appropriate field test to determine the effectiveness of a range of anthelmintics against field populations of nematodes (Johansen, 1989). These limitations include the fact that it is a cumbersome and time-consuming test to conduct both on the farm and in the laboratory, which may largely explain why this test has not been more widely adopted by farmers. A further reason is the failure of farmers to recognise the importance of testing the resistance status of the nematode parasites of their sheep flocks (Besier, 1996). The FECRT is insensitive for the detection of early stages of anthelmintic resistance (Martin et al., 1989), but of good specificity if conducted properly (Geerts and Gryseels, 2001). The FECRT protocol indicates a clinical diagnosis of resistance at a particular percent reduction after treatment; in this study, a reduction of less than 95% was considered diagnostic for resistance. In mixed nematode populations typically encountered in the field the sensitivity of the test can be improved by using faecal larval cultures to identify resistant genera (Lyndall-Murphy, 1993) and by using discriminating dosages of anthelmintic such as the half dose of ivermectin used in this study (Palmer et al., 2001).

The surveyed farmers constitute approximately 2% of WA’s sheep farmers, and could be considered amongst the most progressive due to their adoption of anthelmintic resistance testing. This possible bias, along with the small sample size, would suggest that caution against over interpretation of the findings of the present study is warranted. To minimise the cost of the study only those farmers having conducted a FECRT in the years 1999 and/or 2000 were included in the questionnaire mailing list. However, we note that the prevalence of ivermectin resistance amongst those surveyed in this study is consistent with other recent estimations of its prevalence in WA (Palmer et al., 2001). The potential bias that responders may be more likely than non-responders to have ivermectin resistance was not observed in this study. The response of 56% was good given the length and complexity of the questionnaire. In a similar recent survey of progressive Scottish fanners a response rate of 43% was achieved (Bartley et al., 2003).

5. Conclusion

This survival analysis has identified possible factors contributing to the rapid development of ivermectin resistance on WA sheep farms where routine summer drenching is practised. The present study has highlighted the impact of the farmer’s management of the sheep flock, with development of resistance significantly slower on those farms where a suite of best-practice worm control strategies has been employed. Particular support is provided for the practices of keeping winter drenching to a minimum and the use of safe pastures after drenching.

Acknowledgements

This work was supported by a grant from the Department of Agriculture, Western Australia. The authors wish to acknowledge the assistance of Margaret Setter and Carla Thomas of Murdoch University, and Jill Lyon of the WA Department of Agriculture, with the survey. The cooperation of the veterinarians and consultants and their clients who participated in the survey is also acknowledged.

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