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Regional report

The current status of anthelmintic resistance in a temperate region of Australia; implications for small ruminant farm management

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ABSTRACT

Widespread anthelmintic resistance in small ruminants is a constraint on the profitability of the meat/wool industry. Limited published data is available on the prevalence and efficacy of anthelmintics, particularly in Australia where parasites affecting ruminant systems vary greatly between geographic regions. This paper reports on the anthelmintic resistance status in a temperate region of Victoria, Australia, a major sheep producing state largely affected by *Trichostrongylus* species and *Teladorsagia circumcincta*. The prevalence of anthelmintic resistance to any product was high (71%), with farms reporting varying levels of drug efficacies (21–100%). Resistance to older chemical groups (i.e. fenbendazole and levamisole) and single active macrocyclic lactone treatments was higher than newer chemical groups and combination treatments. This report provides clarity on anthelmintic resistance in the temperate region of Victoria and more importantly suggests that more comprehensive, regional specific anthelmintic resistance studies are required to understand the real level of chemical resistance threatening the effective control of worms.

1. Introduction

The most economically important endoparasites on the Australian and global sheep industries are *Teladorsagia circumcincta* (small brown stomach worm), *Trichostrongylus* species (scour worms) and *Haemonchus contortus* (barber's Pole worm). In Australia, endoparasites are the second biggest economically damaging endemic disease impacting sheep production, with an estimated annual cost of AUD $436 million (Lane et al., 2015). Records from Australia Wool Innovation limited and Meat and Livestock Australia have shown that it the last decade (2008–2017), Australia's national sheep flock has stabilised to ~73.03 ± 2.3 million (AWI, 2019) which equates to the world's third biggest producer of sheep products (meat/wool) and accounts for ~AUD $3 billion in exports (ABARES, 2017). Victoria is responsible for approximately 45% and 39% of Australia's lamb and mutton production respectively (MLA, 2017).

Anthelmintic-treatment remains an integral part of an effective parasite management. However, anthelmintic resistance is an ingrained threat to the effective control of parasites in ruminants worldwide and can develop quickly (Lamb et al., 2017). Integrated parasite management (IPM) programs for regional worm control are important to delay the occurrence of anthelmintic resistance (Kahn and Woodgate, 2012). Anthelmintic resistance management plans include the identification and mitigation of high risk practices, maintenance of an anthelmintic-susceptible worm populations, preventing the introduction of resistant worms, and the optimal choice of anthelmintic-treatment (Leathwick and Besier, 2014). This is particularly important, as resistance to the recently developed monepantel and derquantel/abamectin combination anthelmintics have already been reported (Scott et al., 2013; Sales and Love, 2016; Lamb et al., 2017). Routine efficacy testing of anthelmintic drugs is pivotal to an effective IPM program. The standard procedure for measuring anthelmintic resistance is through an on farm in vivo efficacy test known as the faecal egg count reduction test (FECRT) (Coles et al., 1992). This involves testing representative groups of sheep with one or more anthelmintic treatments while leaving a group untreated as a reference control group. A faecal egg count (FEC) is performed pre- and post-treatment to determine the efficacy of the chemical. A farm where an anthelmintic treatment is recorded with an efficacy of < 95% and a lower confidence interval (CI) < 90% is classified as having resistant worm populations and the treatment as no longer completely effective at the recommended dose rate (Coles et al., 1992).

Recent publications reporting the anthelmintic resistance status in sheep in Australia have most commonly originated from *H. contortus* dominant Australian states such as the northern region of NSW and Queensland (Lyndal-Murphy et al., 2014; Playford et al., 2014; Kozaruk

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et al., 2015). These papers provide valuable insight into the resistance problem for the blood feeding parasitic worm *H. contortus* but little has been published in areas endemic with *T. circumcincta* and *Trichostrongylus* spp. A national survey of anthelmintic resistance using FECRT data collected over a two-year period (2009–2011) which did analyse areas endemic with *T. circumcincta* and *Trichostrongylus* species such as Victoria (Playford et al., 2014), suggested alarming rates of anthelmintic resistance Australia wide. However, the limited amount of trials included in the data set for Victoria (10 or less) may suggest an under sampled representation of the anthelmintic resistance status of these parasites in sheep within this region. Although Victoria has ~20% of the national sheep flock and is one of the world's largest supplier of sheep meat (DEDJTR, 2014) such published surveys are limited. Here, we summarise FECRT data from 66 farms over a six-year period between 2012 and 2018, to present a profile of anthelmintic resistance in a temperate region of Australia, western Victoria.

2. Methods

2.1. Dataset used to analyse FECRT

A historical dataset collected from the company Dynamic Agriculture was used to analyse the prevalence of anthelmintics resistance in Victoria. The data was collected between the years of 2012–2018 and included 95 farms. The dataset for the paper was cleaned to only include farms where both the efficacy and confidence intervals were recorded. This resulted in 65 farms to analyse data for the presence of anthelmintic resistance. Sheep tested were ewe lambs, ~ 16 weeks of age, and usually had not received anthelmintic treatment previously. The breeds in this study were either Merino or Merino cross.

2.2. Faecal egg count reduction test

Faecal egg count reduction tests (FECRT) were carried out as described by the World Association for the Advancement of Veterinary Parasitology (WAAVP) guidelines (Coles et al., 1992) and a list of the chemicals tested on various farms can be found in Table 1. FECRT were performed on farms when the flock of sheep to be tested had a mean FEC of approximately 300 epg or more. This was determined by pooling ~ 2 g of faecal material from 10 to 15 sheep per flock. Next, animals were divided into treatment groups consisting of 12 animals. The animals are selected from the middle section of the sheep flock with every third or fourth sheep selected for the required number of treatment groups. Animals were colour-coded to their respective treatment groups using paint-markers. To ensure the correct treatment dose, 6–10 of the heaviest animals from the whole cohort were weighed and the dosing gun was set to the appropriate dose based on the heaviest animal and in accordance with the manufacturer's label (see Table 1 for treatment doses). Drench guns were calibrated using a 10 ml measuring cylinder to ensure correct dosage. Following treatment, animals were grazed on pasture as one flock and within 10–14 days faeces were collected from all individual sheep for FEC. Briefly, 2 g of faeces was collected from each individual animal within the treatment groups by inserting a 25 mm plastic tube into the rectum. The plastic tube is washed in warm water between animals. For sheep in control, ivermectin and fenbendazole/levamisole (FEN/LEV) treatment groups, faeces was collected in duplicate to provide additional faeces for larval culture (see below). All FEC were conducted using the modified McMaster technique by trained laboratory technicians. The sensitivity of the modified McMaster test was 1 egg = 40 epg. FECRT efficacy calculations were performed using the Microsoft Excel® macro RESO5 using the following equation;

$$\text{Percentage reduction (efficacy)} = 100\left(1 - \frac{\overline{x}_t}{\overline{x}_c}\right).$$

where $\overline{x}_t$ is the mean count of treated sheep and $\overline{x}_c$ is the mean count of untreated (control) sheep.

Resistance to a chemical group was determined as detailed by Cole et al., (1992). For a farm to be declared to have anthelmintic resistance, both the percentage reduction in egg count was < 95% and the lower confidence interval is < 90%. If anthelmintic resistance was classified as suspected than only one of two criteria was met (Coles et al., 1992).

2.3. Larval cultures

Larval cultures were performed on farms that were found to have resistance to FEN/LEV and ivermectin. Control (no drench) animals were also included for direct comparisons. Briefly, 2 g of faeces was collected from each individual animal as described above. The individual samples within each treatment group were pooled, mixed with vermiculite in glass jars and incubated for 5 days at 27°C. After incubation, the glass jars were exposed to light and inverted into a petri dish containing distilled water for 1–2 days. Larvae were collected from the distilled water using a glass pipette and then transferred to a 50 ml plastic container. Aliquots (100 µl) of the larval suspension were then

Table 1
List of anthelmintics tested in the feacal egg count reduction test (FERCT). Products are listed, along with the company details, active ingredients and published mode of action.

Product	Company	Active ingredient/s	Mode of action
Ivomec®	Merial	Ivermectin (0.8 g/l)	Gamma-aminobutyric acid (GABA)/Glutamate -gated chloride channels (GluCL)
Resolute®	Western Stock Distributors	Abamectin (0.8 g/l)	GABA/GluCL
Cydectin®	Virbac	Moxidectin (0.1 g/l)	GABA/GluCL
Zolvix®	Elanco	Monepantel (25 g/l)	ACR-23 nicotinic acetylcholine n(Ach) receptor sub-unit
Duocare®	Virbac	Fenbendazole (40 g/l)/ Levamisole (25 g/l)	β-tubulin/ nAch
Triguard®	Merial	Abamectin (1 g/l)/ Oxfendazole (22.7 g/l)/ Levamisole (33.9 g/l)	GABA/GluCL/ β-tubulin/ nAch
Startec®	Zoetis	Derquantel (10 g/l)/ Abamectin (1 g/l)	nAch receptor /GABA/GluCL
Scandamax®	Coopers Animal Health	Ivermectin (16 g/l)/ Oxfendazole (43.5 g/l)/ Levamisole (80 g/l)	GABAGluCL/ β-tubulin/ nAch
Rametin Combination	Bayer	Napthalophos (800 g/Kg) /Levamisole (80 g/l) / Fenbendazole (50 g/l)	Cholinesterase inhibitor
Rametin-ML®	Bayer	Napthalophos (800 g/Kg) / Abamectin (2 g/l)	Cholinesterase inhibitor/GABA/GluCL
NAPfix®	Jurox	Napthalophos (135 g/l) /lbendazole (25 g/l) /Abamectin (1 g/l)	Cholinesterase inhibitor/ β-tubulin/GABA/GluCL
Tridectin®	Virbac	40g/l Levamisole 25g/l Albendazole 1g/l Moxidectin	nAch /β-tubulin/GABA/GluCL

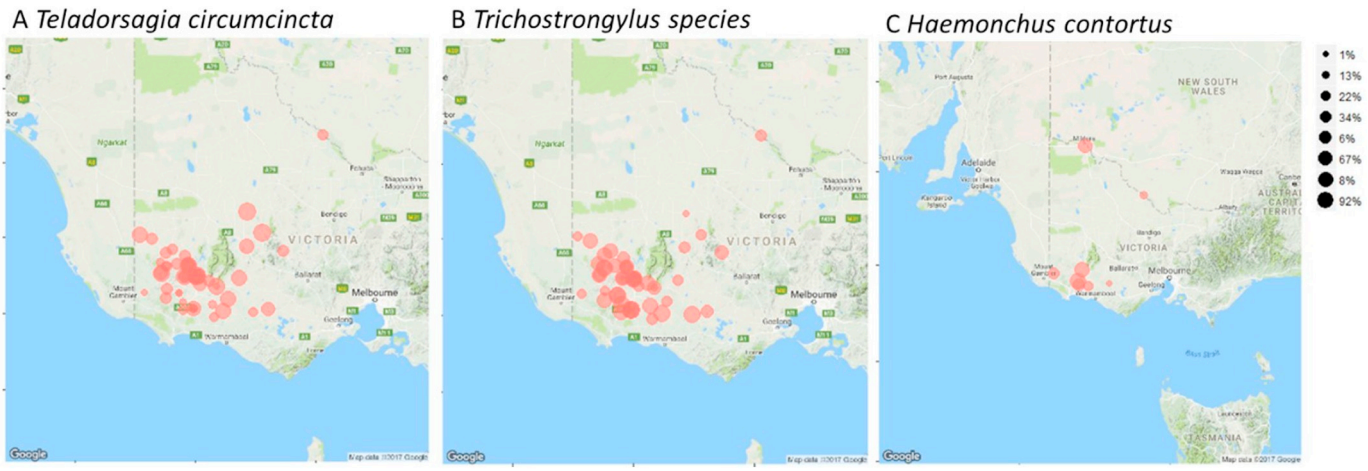

Fig. 1. Regional map of western Victoria indicating the sample collection sites and the distribution of the three strongyloid species; *Teladorsagia circumcictca*, *Trichostrongylus* spp., *Haemonchus contortus*. Size of the data point indicates the percentage of worm species on the given farm.

transferred to microscope slides (in duplicate), fixed with 1% Iodine and analysed at 400× magnification under a compound light microscope. Strongyle species were differentiated for 100 larvae based on tail morphology as described by (van Wyk et al., 2004). Data were converted to a percentage of the total species counted per treatment group.

3. Results

In this study, data from 66 farms were analysed over a six year period for worms with anthelmintic resistance. The predominant worm species on the farms tested were *T. circumcincta* or *Trichostrongylus* spp. with 100% and 98% of farms positive for the two species respectively. Farms positive for *T. circumcincta* ranged from a minimum of 2% of the total worm population to 99%. This was similar to *Trichostrongylus* spp. where it ranged from 1 to 98%. *H. contortus* larvae were only present on 19% of farms tested in this study and ranged from 1 to 67% of the total worm population (Fig. 1).

More than half of the farms reported resistance to the FEN/LEV combination and ivermectin as a single active treatment (58% and 67% respectively; Table 2, Fig. 2). Furthermore, 29% and 24% of farms were found to have susceptible worms to FEN/LEV and ivermectin respectively with 14% and 9% of farms reporting suspected resistance respectively (Fig. 2). The efficacy range was also large with an efficacy mean of 88% and a range of 25%–100% for FEN/LEV and a mean efficacy of 82% and range of 21%–100% for ivermectin (Fig. 3). Of the other macrocyclic lactones (ML) single active anthelmintics, 28% and 10% of farms were reported with resistance and 15% and 14% reported as suspected resistance to abamectin and moxidectin respectively (Table 2, Fig. 2). The rametin combination and rametin-ML combination was ineffective on 18% and 6% of farms tested (Table 2). No resistance was reported against monepantel and combination anthelmintics; derquantel/abamectin, oxfendazole/levamisole/abamectin, napthalophos/albendazole/abamectin and latest product from Virbac, Tridectin® (Table 2). However, there were three reports of suspected resistance to the oxfendazole/levamisole/abamectin combination treatment.

Larval cultures were performed on samples where anthelmintic resistance was detected against FEN/LEV and ivermectin. A high percentage of farms were detected with *T. circumcincta* resistant to both FEN/LEV and ivermectin (93% and 91% respectively, Table 3). Only 62% and 63% of farms reported *Trichostrongylus* resistant species to FEN/LEV and ivermectin respectively (Table 3). No farms were detected with *H. contortus* resistant to FEN/LEV however 56% of farms were detected with resistance to ivermectin (Table 3).

4. Discussion

Despite continual investment in alternative research and development for parasite worm control in small ruminants, anthelmintic treatment is still a major form of control. Even with the implementation of regional IPM programs which involve mixed grazing, spelling paddocks and best practice administration of anthelmintic treatment, resistant worm populations can develop. Hence, continued surveillance and monitoring programs for the detection of anthelmintic resistant

Table 2
The percent of farms detected with anthelmintic resistance from 2012 to 2018 to single and combination anthelmintic products. The percent of farms detected with anthelmintic resistance, defined as efficacy < 95%, CI < 90% (column 4), calculated from the number of farms detected with resistance (column 3)/number of farms tested (column 3).

Product (active ingredients)	Number of farms tested	Number of farms with < 95%FECRT (CI < 90%)	Percent of farms with < 95%FECRT (CI < 90%)
Ivomec (Ivermectin)	55	36	67
Resolute (Abamectin)	65	18	28
Cydectin (Moxidectin)	59	6	10
Zolvix (Monepantel)	28	0	0
Duocare (FEN/LEV)	66	38	58
Triguard (Oxfendazole/LEV/Abamectin)	59	0	0
Startec (Derquantel/Abamectin)	20	0	0
Scandamax (Ivermectin/Oxfendazole/LEV)	6	1	17
Rametin combination (Nap/FEN/LEV)	33	6	18
Rametin-ML® (Nap/Abamectin)	17	1	6
NAPfix® (Nap/Albendazole/Abamectin)	15	0	0
Tridectin (Moxidectin/LEV/Albendazole)	19	0	0

FEN = Fenbendazole, LEV = Levamisole, Nap = Naphthalophos.

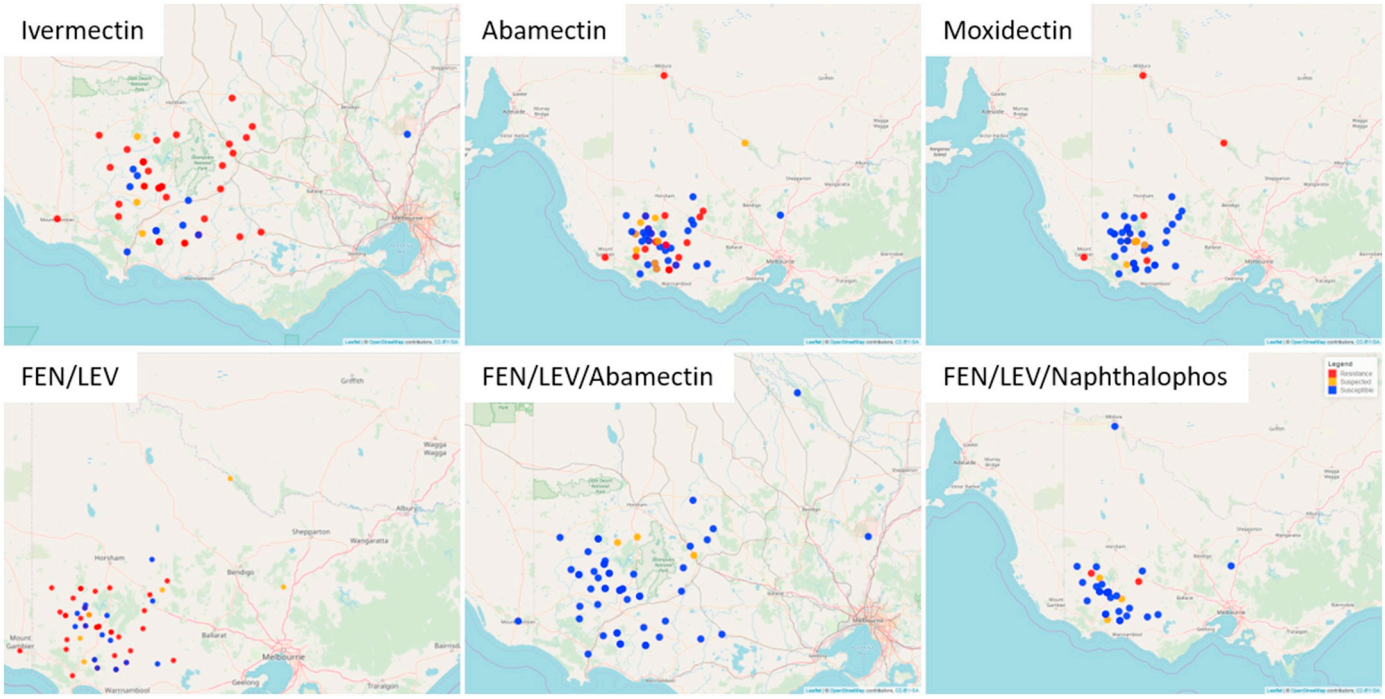

Fig. 2. Regional map of western Victoria indicating the location of farms tested for anthelmintic resistance. For each chemical group, farms have been colour-coded based on the chemical efficacy; red indicating resistance (efficacy < 95%, 95% CI < 90%), orange indicating suspected resistance (either efficacy < 95% or 95% CI < 90% and blue indicated susceptible (efficacy > 95%, 95% CI > 90%). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

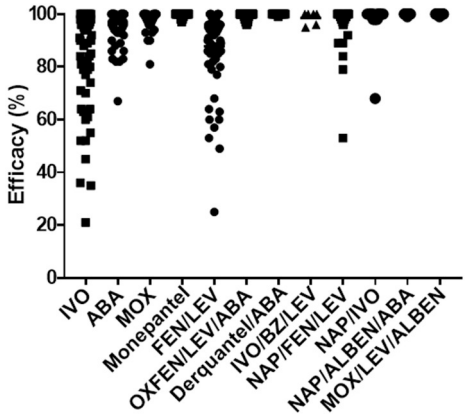

Fig. 3. The efficacy range of anthelmintic products. Each data point represents the efficacy of the respective chemical at eliminating parasitic worm infections on an individual farm.
Abbreviations; IVO = ivermectin, ABA = abamectin, MOX = moxidectin, FEN = fenzabendazole, LEV = levamisole, OXFEN = oxfendazole, ALBEN = albendazole, NAP = naphthalophos.

worm populations are important to ensure the prolonged efficacy of chemicals (Kaplan and Vidyashankar, 2012).

This paper reports on the worm distribution and anthelmintic resistance status of 66 sheep farms, in a temperate region of Australia (western Victoria), tested for anthelmintic resistance as part of an IPM program through a commercial service provider and farm business consultant. The analysis of larval culture results from control sheep allowed the distribution of worm species to be plotted within Victoria (Fig. 1). The data shows that the predominant worm species within western Victoria were *Trichostrongylus* spp. and *T. circumcincta* with isolated pockets of *H. contortus* along the NSW-Victorian border and the southwestern coast line of Victoria. This is consistent with the well-known distribution of these species throughout Australia reviewed by Roeber et al. (2013). During the 6-year period, the distribution of *H. contortus* was particularly high in 2014 which was a year that had above average maximum temperatures (1.53 °C higher; BOM, 2014). This increased incidence of *H. contortus* in western Victoria is consistent with recent distribution predictions that indicate *H. contortus* is spreading more south and westward than traditional regions in the eastern states of Australia (Emery et al., 2016).

While there is a concern with the accuracy of species identification using larval culture between *T. circumcincta* and *Trichostrongylus* spp. as the length dimensions used to distinguish between species overlap (Coles et al., 1992; McMurtry et al., 2000), *T. circumicncta* was found to be the major cause of reduced drug efficacy of FEN/LEV and ivermectin. There were also higher reports of *H. contortus* resistance to ivermectin than the FEN/LEV combination (5/9 cf. 0) farms. However, given the low and sporadic distribution of *H. contortus* within western Victoria, it is difficult to determine whether this increase is a result of a small sample size and it would also be influenced by factors not controlled for in this study such as the drench history on the farms.

Although ivermectin resistance was common (67%; Table 2) among

Table 3
Percent of farms with resistant *Teladorsagia circumcincta, Trichostrongylus* spp., or *Haemonchus contortus* populations. Brackets indicate the number of resistant farms compared to the total farms positive for that species.

	Teladorsagia circumcincta	Trichostrongylus spp.	Haemonchus contortus
Fenbendazole /Levamisole	93% (39/42)	62% (26/40)	0% (0/4)
Ivermectin	91% (40/44)	63% (27/43)	56% (5/9)

the farms tested, lower rates of abamectin and moxidectin resistant farms were detected (28% and 10% respectively, Table 2). Macrocyclic lactones comprise of the avermectins (ivermectin, abamectin and doramectin) and the milbemycins (milbemycin and moxidectin) (NRA, 1998). Ivermectin and abamectin were the first of the macrocyclic lactones to be registered in Australia as new anthelmintics in the mid 1980's (Prichard et al., 2012). Moxidectin was released for use in Australia in 1994 (NRA, 1998) and hence the differences in the prevalence of resistant parasite populations could be explained by frequency of use due to their respective release dates. It could also suggest that the genetic/phenotypic mutation(s) conferring resistance to ivermectin is different to that of abamectin and moxidectin or reflect differences in the pharmacokinetics profiles, as moxidectin which is more lipophilic and has a longer half-life (Prichard et al., 2012). The relatively low level of farms with moxidectin-resistant parasites is encouraging, as a common practice among many sheep producers is to use moxidectin as a long-acting injection (20 g/L Moxidectin) to protect sheep against parasites during the periparturient period (*S. Cotton per. Comm.*). The product claims no < 90 days protection against *H. contortus* and *T. circumcinta* and up to 49 days against *T. colubriformis*, a very common winter worm in south west Victoria (*S. Cotton per. Comm.*).

A national survey of anthelmintic resistance by Playford et al. (2014) who published FECRT performed in Victoria between 2009 and 2012, reported much higher rates of on-farm anthelmintic resistance for macrocyclic lactones. Resistance was reported on 90%, 40% and 67% of farms for ivermectin, moxidectin and abamectin, respectively. The discrepancies in the percent of farms with macrocyclic lactones resistance could be due to the differences in sample size between the two studies (10 FECRT cf. ~66 FECRT). This strongly highlights the need to conduct comprehensive state by state anthelmintic resistance surveys to accurately understand the threat of anthelmintic resistance to effective worm control. In addition, compiling data from smaller geographical regions within each state would be warranted given the differences in distribution of worm species.

The organophosphate anthelmintic, napthalophos, was tested in this study as a combination treatment. All treatments had relatively low rates of farms reporting resistant worms. Rametin® combination originally sold by Bayer is now off the market due to supply issues and has been replaced by the combination drench NAPfix® sold by Jurox. Organophosphates are “old drugs” however are still widely used as insecticides. Safety and environmental concerns surround the use of organophosphates due to associated adverse effects on non-target organisms such as humans and bees either due to acute or chronic exposure (Costa, 2006). There have been at least three farms reporting sheep mortalities across western Victoria with suspected deaths caused by organophosphate either by incorrect administration of the drench or incorrect dose rate or a combination of both (*S. Cotton per. Comm.*). Similar cases of sheep mortality after use caused a voluntary non-urgent recall of the product NAPfix® which underwent vigorous testing with a product re-launch in 2017 under a stewardship program to ensure the correct use of the product (Jurox, 2017 *press release*). The contradictions indicated on the drench labels can preclude the use of these products in younger animals, sheep that are thirsty or exhausted or under a certain age or live-weight and therefore the organophosphate containing products are usually used in mature age sheep.

The three-way combination anthelmintic therapies still appeared to be highly efficacious with no anthelmintic resistance reported for Triguard® (abamectin/oxfendazole/levamisole) and NapFIX® (napthalophos/albendazole/abamectin). The high efficacy rates of the three-way combinations are reassuring as recent reports have shown resistance in *H. contortus* to a four-way combination treatment (Lamb et al., 2017). In northern NSW, an efficacy of 53% was reported for sheep treated with Q-drench® which comprises of abamectin, albendazole, closantel and levamisole hydrochloride with the resistant worms recovered all being *H. contortus* (Lamb et al., 2017). Furthermore, in New Zealand anthelmintic resistance has been reported to the abamectin, benzimidazole and levamisole combination drench in lambs at seven months of age with an 85% efficacy rate reported against *Trichostrongylus* spp. (Hodgson and Mulvaney, 2017). It is interesting to note the high efficacy of the triple combination treatment which contains oxfendazole, levamisole and abamectin as the three active ingredients (100%; $n = 59$; Table 2). This is despite the high prevalence of worm resistant populations found to the benzimidazole/levamisole based combination treatment (Duocare®) and 28% of farms reporting worms resistant to abamectin. Hence, it seems that combining the compounds has greatly increased the efficacy of the product at eliminating worm infections.

No resistant parasites were detected against the newest groups of anthelmintics (monepantel and derquantel). Recent reports have identified monepantel resistant parasite populations in sheep including *H. contortus*, *T. colubriformis* and *Oesophagostomum* spp. (Cintra et al., 2016; Sales and Love, 2016). In addition, a reduced efficacy of 94% to the derquantel/abamectin combination anthelmintic has been reported on one farm in the *H. contortus* dominated sheep production area of northern NSW (Lamb et al., 2017). Regular monitoring of the efficacy of the newer groups of anthelmintics will be necessarily to ensure that effective worm control measures are maintained. Prolonging the effectiveness of anthelmintics largely relies on producers continuously monitoring parasite burdens through faecal egg counts. Although this method is laborious, faster and more accurate methods have been developed. In particular, the use of detecting parasite DNA from the faeces and the development of automated egg counters (Roeber et al., 2012; Bisset et al., 2014; Roeber and Kahn, 2014; Slusarewicz et al., 2016). The adoption of these practices once feasible will aid in the practice of constant FEC monitoring. This is also important to ensure that animals are exposed to a low level of infection so that immunity can develop and parasite resistant traits can be breed into sires, further reducing the reliance on chemical control.

5. Conclusions

Throughout western Victoria, highly variable levels of on-farm anthelmintic resistance were observed. Some farms reported no resistance, while other farms reported resistance to > 4 different products. This poses the question of what practices are being performed on what farms to either speed up or slow down the development of chemical resistance. Major drivers of anthelmintic resistance are practices that promote treatment on low worm contaminated pastures such as the ‘summer-drenching program’ promoted in Mediterranean climate zones (Leathwick and Besier, 2014). Surveys concerning how sheep producers are making decisions on how/when/what to treat their animals combined with management practices following treatment will aid in identifying practices either delaying or promoting resistance within this region. Constant surveillance of anthelmintic resistance will be vital for the optimal control/delay of anthelmintic resistance on farm. Importantly, this study suggests that more comprehensive, production system specific anthelmintic resistance surveys are required to understand farm management practices and how they contribute to the level of chemical resistance threatening the effective control of worms. Particularly, understanding reasons why some farms report no resistance to any product tested while other farms report resistance to multiple products.

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Ethical statement

Nothing to dislosure.

Conflict of interests

None.

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