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Research Paper

Anthelmintic resistance in cattle: A systematic review and meta-analysis

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ABSTRACT

A systematic review and meta-analysis was conducted to identify, evaluate, and synthesize primary literature reporting the efficacy of anthelmintic drugs in cattle. Information on the bibliographic data, anthelmintic drugs, animals, reduction method, days after application, parasite genera, type of application, and dosage were collected. The final data base was composed of 70 articles published between 1986 and 2016 with a total of 8,976 animals. The mode of application interfered with the efficacy of anthelmintic drugs in cattle ($P < 0.05$); oral application was superior to injectable and pour-on drugs. The combined use of drugs was superior to single macrocyclic lactones including ivermectin ($P < 0.05$), in this way the combined use was more effective than the single use of drugs for the control of gastro-intestinal nematodes in cattle ($P < 0.05$). Nematode genera in the abomasum (*Ostertagia* spp., *Haemonchus* spp.) and intestine (*Cooperia* spp.) were evaluated. Levamisole had a greater efficacy for *Cooperia* spp. than *Ostertagia* spp. ($P < 0.05$); ivermectin had a greater efficacy for *Ostertagia* spp. than *Haemonchus* spp. ($P < 0.05$); doramectin had a greater efficacy for *Ostertagia* spp. than *Cooperia* spp. ($P < 0.05$). Dosing in larger quantities and according to the manufacturer's recommendation was most efficient, and the dose limiting species differed between substance classes. The test based on the count of eggs per gram of faeces indicated a reduced efficacy of the drug as days passed following treatment. The forest plot did not show a difference ($P > 0.05$) between interventions (resistance and efficacy). The results of this systematic review and meta-analysis suggest that anthelmintic resistance in cattle is present on several continents. Therefore, there is a need to replace the schemes based on the exclusive use of drugs in order to decrease the selection pressure.

1. Introduction

Infections caused by gastro-intestinal nematodes (GIN) in the extensive system of livestock can cause serious economic problems (Demeler et al., 2009). This fact can be attributed to impaired animal health due to the presence of GIN, resulting in decreased production of meat and milk. To control these infections, anthelmintic drugs have been used for almost 40 years (Geurden et al., 2015). The classes of broad-spectrum anthelmintics range from benzimidazoles (BM), imidazothiazoles (IM)/tetrahydropyrimidens and macrocyclic lactones (ML), but salicylanilides, phenolic substitutes and organophosphates are also used (Molento et al., 2004). Broad-spectrum anthelmintics are more commonly used in ruminants because they are capable of eliminating large numbers of parasites, besides being of easy administration and safe to the hosts (Monteiro, 2011). However small-spectrum anthelmintics (salicylanilides, phenolic substitutes and organophosphates) have less use because they act in adults worms and partially in the immature stages of *Fasciola hepatica* (Oliveira-Sequeira and Amarante, 2001). Some also exert activity against hematophagous nematodes such as *Haemonchus* spp. (Taylor et al., 2010).

Anthelmintic resistance (AHR) in GIN can however arise (Stafford et al., 2010) due to risk factors associated to the use of anthelmintic, such as under-dosage (Maciel et al., 1996), overuse, and use of the same chemical compound without rotation. Sampling procedures for egg count per gram of feces (EPG) before and after application of a drug allow observing if AHR is present. If either percentage reduction in EPG is less than 95% or the 95% confidence level of EPG is less than 90%, AHR is suspected (Coles et al., 1992).

Occurrence of AHR against anthelmintics is an emerging problem in all parts of the world (Demeler et al., 2009), with some regions having particular large rates of AHR. In New Zealand, 90% of farms had AHR in 2005, but large AHR rates are also increasingly found in parts of Brazil, Argentina and Europe (Sutherland and Leathwick, 2011).

In recent years, several studies have been performed to investigate AHR in cattle. While all these studies may provide valuable isolated information, they sometimes describe conflicting results. One way to qualify and quantify such findings is through a systematic review (SR) and meta-analysis (MA) approach, which allows for the analysis and systematization of information. This type of approach combines the findings of several studies to make a reproducible summary of their

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Table 1
Population and outcome search term strings used for the final search in the systematic review of anthelmintic in cattle infected by gastrointestinal nematodes.

Acronym	Search string
Population	("cattle" OR "calves") ("beef" OR "dairy")
Outcome	(anthelmintic OR "macrocyclic lactone*" OR ivermectin OR moxidectin OR doramectin OR levamisole OR fenbendazole) AND (gastrointestinal OR internal) AND (parasite OR nematode OR worms OR worming) AND (resistance OR resistant) AND (efficacy OR effectiveness) AND (faecal egg count reduction test OR FECRT) AND (route of administration" OR "injectable formulation" OR oral OR pour on) AND ("natural infections")

data (Lovatto et al., 2007), providing the most substantive clinical evidence (Moher et al., 2010), based on defined methods that guide the search and inclusion criteria (Sargeant et al., 2006).

The aim of this SR-MA was to identify, evaluate, and synthesize primary literature reporting AHR of GIN in cattle. The rationale for this study was to generate information to help producers make evidence-based decisions and recommendations for a sustainable use of anthelmintic drugs.

2. Materials and methods

2.1. Systematization of information: Selection of articles

A systematic literature search was conducted in PubMed (Medline), Web of Science, and Google Scholar for publications made available through the State University of Ponta Grossa by the CAPES portal (*Periodicos da CAPES)*. All search terms are listed in Table 1. The information was extracted from the material and methods section and tables.

Studies were carefully evaluated according to their quality and relevance. At this stage, the information contained in each study was analyzed with regard to the experimental design, treatments and data analyzed. The main criterion for inclusion of the articles in the meta-analysis was the percentage of worms killed by the drug administered, to analyze the efficacy of anthelmintic drugs. Based on this criterion, the studies were selected by an evaluator, which was selected after training with an experienced professional. The results of the studies, i.e., either positive or negative effects of anthelmintics on GIN, were not used as selection criteria to create the database.

2.2. Tabulation and coding

Data were inserted into the Microsoft Excel (2010), where each line represented a treatment, and each column represented an exploratory parameter. The first variables were related to the bibliographic data (authors, year, periodical, country and home institution), followed by information about the animals (number of animals), the reduction methods (EPG counting or necropsy), days after application of anthelmintic drugs for EPG recount, mode of application (oral, injectable or pour-on), and dosage. Environmental characteristics and information about feed were not tabulated due to the information scarcity in most articles. Herds were not separated by the productive system, as the studies referred to beef and dairy cattle. Negative efficacy values were considered zero in the present study. The experimental characteristics are shown in Table 2.

Data from the database were evaluated based on either the entire dataset or portions of it. Efficacy of anthelmintics were analyzed for combination and unique drugs based on the entire dataset. For more specific analysis, the active principles were separated into ivermectin; doramectin; moxidectin (ML), levamisole (IM), fenbendazole (BM), or combinations: (i) eprinomectin and levamisole; (ii) moxidectin and levamisole; (iii) ivermectin and levamisole; (iv) doramectin and fenbendazole; (v) closantel and levamisole; (vi) moxidectin and albendazole; (vii) eprinomectin and fenbendazole; (viii) ivermectin and abamectin; (ix) doramectin and closantel; and (x) albendazole and closantel. The chemical groups of the respective active principle were tabulated to obtain a broader view of the effectiveness of the drugs most used around the world (i.e., ML, IM, BM and combinations).

2.3. Database description

The initial SR was composed of 150 publications of which 70 publications published between 1986 and 2006 were retained for further analysis, totaling 8,976 cattle. Publications were excluded if studies did not report the reduction percentage values of EPG, related to other animal species (sheep, goats, pigs), or used homeopathic products and artificial infections.

In the final database, 41% of the studies were executed in South America, 25% in North America, 14% in Oceania, 12% in Europe, 2% in Asia, 1% in Central America and Africa. With regard to the mode of application, injectable drugs were most often studied (51%), followed by a combination of modes of application (25%), pour-on (13%) and oral (9%) application. Initial and final EPG count was the most frequently used reduction method (85%), followed by count of larvae in the gastrointestinal system through necropsy (15%), and one study in which both procedures were applied.

The main GIN included in the final database were *Ostertagia* spp., *Trichostrongylus* spp., *Cooperia* spp., *Haemonchus* spp., *Oesophagostomum* spp., and multiple species. The dosage ranged for levamisole from 0.2 to 10.0 mg/kg, for moxidectin from 0.2 to 1.0 mg/kg, for ivermectin from 0.2 to 0.63 mg/kg, for doramectin from 0.2 to 0.7 mg/kg, for fenbendazole from 5 to 7.5 mg/kg and for combinations of drugs from 0.2 to 15.5 mg/kg of bodyweight.

2.4. Statistical analysis

A graphical analysis was used as a first step to evaluate the distribution, coherence and heterogeneity of the data (Lovatto et al., 2007). Through this analysis, hypotheses of relations were performed to define the statistical model. The definition of dependent and independent variables and the coding of data, that allows analysis of inter- and intra-experimental effects, were performed according to Lovatto et al. (2007) and Sauvant et al. (2008). Passive variables were submitted to analysis of variance and comparisons by Tukey test: i.e., the mode of application (oral, injectable or pour-on), chemical group, active principle, type of use (combination or unique), reduction method (EPG or necropsy). The GIN genera were analyzed separately for each active principle. The publication number was fixed in all analyses to exclude possible random effects. An analysis of prevalence of AHR for each anthelmintic family was made for continent by descriptive statistics. Prediction equations were developed from the coefficients obtained using the variance–covariance analysis. The equations were performed to evaluate the behavior of anthelmintic efficacy in relation to the days after application to recount of EPG and dosage. The analyses were performed using the program Minitab 17 (Minitab Inc., State College, USA).

A forest plot was made according to Neyeloff et al. (2012) in Microsoft Excel (2007) to analyze the efficacy of anthelmintic against GIN for each study based on the number of events and sample size. The forest plot represents all selected studies (n = 70) with confidence intervals of effect size at 95% illustrated by horizontal lines. The central line represents studies with no difference between interventions and separates the graph in studies with resistance (left side) and efficacy

Table 2
Database description of selected studies in the systematic review and meta-analysis of cattle infected by gastrointestinal nematodes.

N*	Authors	Continent	Animals	Age, months	Mode of application**	Reduction method***
1	Abdellati et al. (2010a)	Europe	330	12	I	E
2	Abdellati et al. (2010b)	Europe	46	5.5	I/O	E
3	Anziani et al. (2004)	South America	40	6.5	I	E
4	Arantes et al. (1995)	South America	14	10	I	E
5	Areskog et al. (2013)	Europe	1620	-	P	E
6	Ballweber (1997)	North America	103	9	I/P	E
7	Bianchin et al. (1993)	South America	20	12	I	D
8	Borges et al. (2015)	South America	18	10	I	D
9	Bullen et al. (2016)	Oceania	300	7	I	E
10	Cezar et al. (2010)	South America	149	12	-	E
11	Cleale et al. (2004)	North America	100	12	I	E
12	Conder et al. (1998)	North America	490	-	P	E
13	Condi et al. (2009)	South America	20	12	I	E
14	Costa et al. (1986)	South America	21	-	O	E
15	Costa et al. (1996)	South America	14	10	I	E
16	Cotter et al. (2015)	Oceania	45	10.5	I/O	E
17	Coumendouros et al. (2003)	South America	40	9.5	P	E
18	Demeler et al. (2009)	Europe	400	-	I	E
19	Diaz et al. (2015)	North America	500	5.5	I	E
20	Diez et al. (2005)	North America	30	-	P	E
21	Eddi et al. (1993)	South America	20	-	I	D
22	Eddi et al. (1997)	South America	60	12	I/P	D
23	Fazzio et al. (2014)	South America	56	4.5	I	E
24	Fazzio et al. (2016)	South America	54	6.5	I	E
25	Felippelli et al. (2014)	South America	144	9	I	D
26	Fielet al. (2001)	South America	60	10	I/O	E
27	Francener et al. (2008)	South America	100	-	-	E
28	Gasbarre et al (2009a)	North America	171	-	P/I/O	E
29	Gasbarre et al. (2009b)	North America	143	10	I/P/O	E
30	Geerts et al. (1987)	Europe	12	-	I/O	E
31	Geurdent al. (2004)	Europe	22	9.5	I	E
32	Geurden et al. (2015)	Europe	753	-	I	E
33	Holsback et al. (2015)	South America	16	-	I	E
34	Hooke et al. (1997)	Oceania	80	7	I/P/O	E
35	Hosking et al. (1996)	Oceania	28	-	O	E
36	Jackson et al. (1987)	Oceania	24	2	O	E
37	Ku et al. (2012)	North America	301	8	I	E
38	Leathwick and Miller (2013)	Oceania	210	-	I/P/O	E
39	Lima et al. (1995)	South America	20	12.5	I	D
40	Guerra Llorensl et al. (2014)	Central America	200	12	I	E
41	Lopes et al. (2014)	South America	48	9	P	D
42	Loveridge et al. (2003)	Oceania	18	7	P	D
43	Lyndal-Murphy et al. (2010)	Oceania	54	6	O/P	E
44	Mason and Mckay (2006)	Oceania	75	6	P	E
45	Mello et al. (2006)	South America	70	11	I	E
46	Mena et al. (2008)	North America	52	9	I	E
47	Miller and Morrison (1992)	North America	39	9	I/O	E
48	Morin et al. (1997)	North America	30		P	E
49	Nava et al. (2014)	North America	278	5.5	I	E
50	Ogunsusi et al. (1986)	Africa	10	19	I	E
51	Pinheiro et al. (1999)	South America	88	-	I	D
52	Rafiq et al. (2004)	Asia	48	60	O	E
53	Ramos et al. (2016)	South America	119	8	I/P	E
54	Rangel et al. (2005)	South America	80	8	I	E
55	Ranjan et al. (1992)	North America	25	7.5	I	E
56	Romero et al. (2009)	North America	24	8	I	E
57	Sievers and Fuentealba (2003)	South America	72	12	I	E
58	Sievers and Alocilla (2007)	South America	36	7.5	-	E
59	Silva and Avalia (2009)	South America	48	-	I	E
60	Skogerboe et al. (2000)	North America	108	8	P	E
61	Soutello et al. 2007	South America	194	-	I	E
62	Stafford and Coles (1999)	Europe	13	-	I	E
63	Suaez and Cristel (2007)	South America	45	9	I/O	E
64	Toma et al. (2008)	South America	40	11	-	E
65	Valladares et al (2015)	Europe	200	-	I	E
66	Waghorn et al. (2016)	Oceania	210	-	O	E
67	Williams et al. (1997)	North America	72	8	I/P	E
68	Yadav and Verma (1997)	Asia	21	9	O	E
69	Yazwinski et al. (2009)	North America	60	6.5	I/O	E
70	Yazwinski et al. (2013)	North America	25	5	I/P	D

* N: study number.
** Mode of application: I: injectable; O: oral; P: pour-on.
*** Reduction method: E: eggs per gram of faeces; D: death (necropsy).

Table 3
Average values of efficacy (%) in relation to mode of application, anthelmintic drug (group), active principles, type of use and reduction methods in cattle infected by gastrointestinal nematodes.

Variables	N*	Efficacy (%)	P (value)
Mode of application			
Oral	194	90 a	P = 0.00
Injectable	890	78 b	
Pour on	279	77 b	
Group			
Combinations	84	90 a	P = 0.00
Imidazotiazoles	169	89 a	
Benzimidazoles	192	85 a	
Macrocyclic lactone	913	76 b	
Active principles			
Combinations	84	90 a	P = 0.00
Moxidectin	145	89 a	
Levamisole	150	88 a	
Fenbendazole	127	87 a	
Doramectin	172	84 a	
Ivermectin	496	71 b	
Type of use			
Combinations	84	90 a	P = 0.00
Unique	1321	78 b	
Reduction methods			
EPG	1296	80 a	P = 0.00
Necropsy	109	69 b	

* N: number of treatments.
Different letters in the same column indicate statistical difference by Tukey test ($P < 0.05$).

(right side). Horizontal lines crossing the central tendency line indicate no difference between interventions ($P > 0.05$). In the last line of the graph, the summarized value is shown. Statistical heterogeneity was made using I^2, which describes the proportion of total variation in cross studies attributed to heterogeneity.

3. Results

Mode of application interfered ($P < 0.05$) with the efficacy of anthelmintic drugs in cattle. Efficacy of orally applied drugs (90%) was superior to that of injectable (78%) and pour-on drugs (77%). Injectable drugs did not differ ($P > 0.05$) from pour-on drugs (Table 3).

Among the chemical groups analyzed (Table 3), greatest average efficacy rates were found in IM (89%), BM (95%), and combinations of chemical groups (90%), which differed ($P < 0.05$) from those of ML (76%). Similar results were observed for the active principle, as they are inherent to the chemical group (Table 3). Combinations of active principles (90%), moxidectin (89%), levamisole (88%), fenbendazole (87%) and doramectin (84%) had greater average efficacy rates, which differed ($P < 0.05$) from those of ivermectin (70%).

The type of use of anthelmintic drugs interfered ($P < 0.05$) with their efficacy (Table 3), with a greater average efficacy rate (90%) for a combined than unique use of drugs (78%). The composition of all combinations with the average efficacy rate and dose of each drug is shown in Table 4.

The most commonly used reduction method was EPG, which had a greater ($P < 0.05$) efficacy (80%) than necropsy (69%) (Table 3). The genera of GIN (Table 5) were evaluated in relation to their active principle. Efficacy rates of the active principle levamisole were greatest on *Cooperia* spp. (91%) and *Trichostrongylus* spp. (91%), and lowest ($P < 0.05$) on *Ostertagia* spp. (73%). Efficacy rates of moxidectin on GIN were not significantly different among the parasite genera evaluated. Efficacy rates of ivermectin was greatest on *Ostertagia* spp. (94%) and lowest ($P < 0.05$) on *Haemonchus* spp. (60%). Efficacy rates of doramectin were greatest on *Ostertagia* spp. (89%) and lowest ($P < 0.05$) on *Cooperia* spp. (70%). Efficacy rates of fenbendazole and combinations on GIN were not significantly different among the parasite genera evaluated.

Prevalence of AHR of ML was found in South America, Oceania, Europe and North America (63%, 81%, 82% and 85% respectively).

Table 4
Composition of all combinations, efficacy (%), mode of application, concentration (%), and dose of each anthelmintic drug administered in cattle infected by gastrointestinal nematodes*.

Combinations	N**	N***	Efficacy (%)****	Mode of application	Concentration (%)	Dose
Moxidectin	4	40	97	Injectable	1.0%	0.2 mg/kg
Levamisole				Injectable	7.5%	3.75 mg/kg
Moxidectin	4	40	88	Injectable Injectable	1.0%	0.2 mg/kg
Albendazole					15%	3.4 mg/kg
Albendazole	4	40	78	Injectable	15%	3.4 mg/kg
Closantel				Oral	10%	10 mg/kg
Doramectin	4	40	82	Injectable Oral	1.0%	0.2 mg/kg
Closantel					10%	10 mg/kg
Doramectin	4	40	91	Injectable Oral	1.0%	0.2 mg/kg
Fenbendazole					10%	5.0 mg/kg
Levamisole	4	40	90	Injectable Oral	7.5%	3.75 mg/kg
Closantel					10%	10 mg/kg
Eprinomectin	2	19	99	Pour-on	0.5%	500 µg/kg
Levamisole				Injectable	13.65%	40 µg/kg
Eprinomectin	2	19	87	Pour-on	0.5%	500 µg/kg
Fenbendazole				Oral	10%	5 mg/kg
Ivermectin	48	75	96	Pour-on	1%	500 µg/kg
Levamisole				Pour-on	–	10 mg/kg
Ivermectin	6	27	83	Injectable	2.25%	400 mcg/kg
Abamectin				Injectable	1.25%	250 mcg/kg

* Information extracted from the database.
** N: number of treatment.
*** N: number of treated animals.
**** Mean values of efficacy obtained by analysis of variance.

Table 5
Nematode genera found after treatment with levamisole, moxidectin, ivermectin, doramectin, fenbendazole, combinations, and average of anthelmintic efficacy (%) in cattle infected by gastrointestinal nematode.

Nematode (genera)	N*	Efficacy (%)	P (value)
Levamisole			
Cooperia spp.	39	91 a	P = 0.00
Trichostrongylus spp.	25	91 a	
Multiple species	50	84 a b	
Haemonchus spp.	6	81 a b	
Ostertagia spp.	55	73 b	
Moxidectin			
Ostertagia spp.	2	100	NS
Oesophagostomum spp.	2	99	
Trichostrongylus spp.	11	96	
Haemonchus spp.	9	91	
Multiple species	183	87	
Cooperia spp.	13	86	
Ivermectin			
Ostertagia spp.	23	94 a	P = 0.00
Oesophagostomum spp.	17	90 a	
Trichostrongylus spp.	26	83 a b	
Multiple species	294	72 b	
Cooperia spp.	137	67 b	
Haemonchus spp.	34	60 b	
Doramectin			
Ostertagia spp.	27	89 a	P = 0.00
Mixed infection	67	87 a b	
Truchostrongylus spp.	18	86 a b	
Oesophagostomum spp.	9	84 a b	
Haemonchus spp.	16	73 a b	
Cooperia spp.	45	70 b	
Fenbendazole			
Haemonchus spp.	13	99	NS
Multiple species	32	86	
Ostertagia spp.	37	83	
Cooperia spp.	20	78	
Trichostrongylus spp.	5	67	
Combinations			
Haemonchus spp.	2	100	NS
Cooperia spp.	19	95	
Trichostrongylus spp.	13	94	
Ostertagia spp.	17	94	
Mixed infection	33	82	

* N: number of treatments.
Different letters in the same column indicate statistical difference by Tukey test ($P < 0.05$).

Prevalence of AHR of BM was similar among Central America, North America, Oceania and Africa (80%, 82%, 84% and 91% respectively), for IM the AHR was detected in North America, South America and Oceania (90%, 90% and 91%, respectively) (Table 6).

Various dosages of anthelmintic drugs were used in the studies. In the present study, anthelmintic efficacy was predicted for levamisole, as it was the only active principle with a significant difference in the active principle ($P < 0.05$). The prediction equation (efficacy (%) = 35.24 + 9.30 × levamisole) suggested that anthelmintic efficacy increased by 9.30% for each mg of levamisole added. The days after treatment (i.e., the time point at which EPG was conducted following a drug treatment) determined efficacy rates of drugs ($P < 0.05$). The prediction equation (efficacy (%) = 80.51 − 0.10 × day) suggested that efficacy decreased by 0.10% with each passing day after treatment

The forest plot in Fig. 1 highlights the variability among the selected studies. Twenty-five studies showed AHR ($P < 0.05$), contrasting with seven studies that not showed AHR ($P < 0.05$). The others studies ($n = 38$) showed no difference ($P > 0.05$) efficacy and resistance. In the last line of the graph, the summarized value is shown, which suggests that there was no difference among interventions ($P < 0.05$).

4. Discussion

Infections caused by GIN in grazing cattle have important economic repercussions to the cattle industry worldwide. Several methods were described in literature to prevent AHR within a herd. Avoiding routes of administration with low bioavailability has been suggested (Leathwick and Luo, 2017). The better efficacy was found with orally applied than injectable or pour-on drugs. A study on moxidectin efficacy administered by different routes confirmed that oral application resulted in greater efficacy when compared to injectable and pour-on (Leathwick and Miller, 2013). Oral application was recommended most often because injectable drugs may result in a temporary suppression of the nematodes egg production, which complicates the interpretation of the results (Sutherland and Leathwick, 2011). The lower efficacy of pour-on drugs may be attributed to climatic factors (Sargent et al., 2009), and to issues related to animals inadvertently ingesting drugs through their contact with treated animals (Bousquet-Mélou et al., 2011). Reinemeyer and Cleale (2002) compared the efficacy of injectable and pour-on moxidectin in calves and found large efficacy rates of more than 95% for both methods. The high efficacy of pour-on drugs was attributed to the type of housing, as confinement can lessen the detrimental effects related to the climate. Certain climate conditions may favor the development of nematodes. Simultaneously, the immune system response to infections resulting from the increased presence of nematodes may be reduced due to stress associated to unfavorable climate conditions such that AHR to drugs will augment (Amarante, 2014).

Anthelmintic resistance of GIN was shown to be an issue in several continents (Sutherland and Leathwick, 2011). Efficacy of the drugs might be improved by combining multiple drugs rather than administering a unique drug (Barneset al., 1995). According to Leathwick (2012), this practice can be beneficial if used rationally, despite a certain degree of lateral resistance between drugs of the same chemical group. Gasbarre et al. (2009a) observed inefficacy of levamisole for the genera *Ostertagia* spp.; however, when combined with eprinomectin, the drug showed promising results with regard to nematode control, in the case studied, so the levamisole has no effect on *Ostertagia* spp. (i.e. is tolerant to this drug) whereas eprinomectin have. There is evidence that several nematodes genera are resistant to ML, BM and IM (Sutherland and Leathwick, 2011), which was also observed in the present study.

Most studies reported the presence of multiple species of nematodes, but specific considerations with regard to some active principles were discussed. The low efficacy of levamisole for *Ostertagia* spp. was reported in a former review by Prichard (1994), where AHR was found in Australia and the Netherlands.

An earlier review on the efficacy of ivermectin in cattle by Campbell and Benz (1984) confirmed high efficacy for the majority of GIN found in cattle (*Haemonchus* spp., *Ostertagia* spp., *Trichostrongylus* spp., *Cooperia* spp., and *Oesophagostomum* spp.). Our study suggests, however, a low effectiveness of ivermectin for most nematodes genera. This effect might be explained by a possible overuse of ivermectin over the years. Resistance of *Cooperia* spp. against ivermectin was found to be relatively common and widespread (Kaplan and Vidyashankar, 2012). Other active principles such as doramectin, ivermectin and moxidectin had an equally low efficacy on *Cooperia* spp. (70%, 67% and 86%, respectively). In New Zealand, most cases of resistance to ML involved these particular genera (Sutherland and Leathwick, 2011).

Table 6
Anthelmintic efficacy per continent of macrocyclic lactone, benzimidazoles and imidazothiazoles against gastrointestinal nematodes in cattle.

Continent	Macrocyclic lactone N*	N*[1]	Efficacy** (%)	Anthelmintic resistance***	St Dev****	Minimum	Maximum
Africa	1	5	100	N	-	100	100
Asia	-	-	-	-	-	-	-
Central America	20	200	98	N	0.91	97	100
North America	158	1.707	85	Y	24.40	0	100
South America	343	1.741	63	Y	37.22	0	100
Europe	173	2.141	82	Y	22.97	0	100
Oceania	218	2.019	81	Y	29.06	0	100
Benzimidazoles							
Africa	-	-	-	-	-	-	-
Asia	3	25	84	Y	2.24	83	100
Central America	-	-	-	-	-	-	-
North America	24	79	82	Y	9.51	62	90
South America	4	489	98	N	1.27	97	100
Europe	7	13	100	N	0	100	100
Oceania	5	25	84	Y	24.16	0	100
Imidazothiazoles							
Africa	-	-	-	-	-	-	-
Asia	-	-	-	-	-	-	-
Central America	-	-	-	-	-	-	-
North America	12	170	90	Y	16.21	42	100
South America	24	319	90	Y	17.74	34	100
Europe	-	-	-	-	-	-	-
Oceania	128	713	91	Y	18.88	4	100

* N number of treatments.
*[1]N number of treated animals;**Efficacy: percentage reductions of gastro-intestinal nematodes in cattle.
*** Anthelmintic resistance: Y: yes (< 95% reduction by arithmetic means) N: No (> 95% reduction by arithmetic means).
**** St Dev: Standard deviation.

Studies about prevalence of AHR in different continents were found (Rose et al., 2015; Waller, 1994), but only with qualitative data, which does not allow us to make a comparison with our results.

The diagnostic method for AHR determination is important as it allows quantifying the values to implement the proper disease control management. The faeces test using the McMaster technique (Gordon and Whitlock, 1939), and the coproculture test (Roberts and O'Sulivan, 1950) are more accessible tests than the necropsy test. The necropsy test consists of several steps and can only be conducted on culled animals (Coumendouros et al., 2003). Moreover, the EPG test has a high correlation between the actual presence of nematodes and the predicted values obtained through this test (Bricarello et al., 2007).

Underdosing may cause increased AHR (Lespine et al., 2012). Our results indicate that efficacy of levamisole increased proportionally with increasing dosing, indicating a correct administration of anthelmintic drugs in most studies. A recent study by Leathwick and Luo (2017) evaluated the change in gene frequency at different dosing rates and concluded that AHR was increased at a lower and more variable dose.

In the present study, the dose-limiting species differed among substance class. For ML substances, AHR in cattle was mainly observed for *Cooperia* spp, in line with other studies (Bartley et al., 2012; Leathwick and Miller, 2013; McArthur et al., 2011), and to a far lesser extent for *Ostertagia* spp.

Numerous studies showed variations among the intervals of days for EPG recounting, which may interfere with the test results. Gasbarre et al. (2009a) demonstrated that an interval of 7 days may be insufficient for a complete efficacy of ivermectin. Our results showed that the efficacy decreased as the days passed after application with anthelmintics. To avoid inaccurate diagnosis, it is suggested to perform the EPG recount between days 17 and 21 following application with anthelmintics as egg production by nematodes that survived the treatment is temporarily stopped (Condi et al., 2009).

The use of forest plots in a systematic review in agriculture is scarce; however, this approach is commonly applied in medicines. A forest plot was efficient to demonstrate that a high frequency of treatment was a significant risk factor for AHR in sheep in the study of Falzon et al. (2014), as in our study, the forest plot was efficient to demonstrate a high amount of studies evidencing the AHR worldwide.

5. Conclusion

The SR-MA confirmed that AHR in cattle is widely present in several continents and highlighted risk factors related to the control of GIN in cattle. Factors related to management may influence drug efficacy. Oral application of drugs was shown to be more efficient in cattle compared to injectable and pour-on drugs. The combined use of drugs was superior to single ML including ivermectin. Anthelmintic resistance was demonstrated for most genera of GIN with different types of drugs. Dosing in larger quantities and according to the manufacturer's recommendation was most efficient with levamisole as the active principle. The dose limiting species differed between substance classes. Based on the EPG test, efficacy of drugs diminished as days passed following treatment with drugs.

Conflict of interest statement

The authors: Barbara Haline Buss Baiak; Cheila Roberta Lehnen and Raquel Abdallah da Rocha declare no conflict of interest.

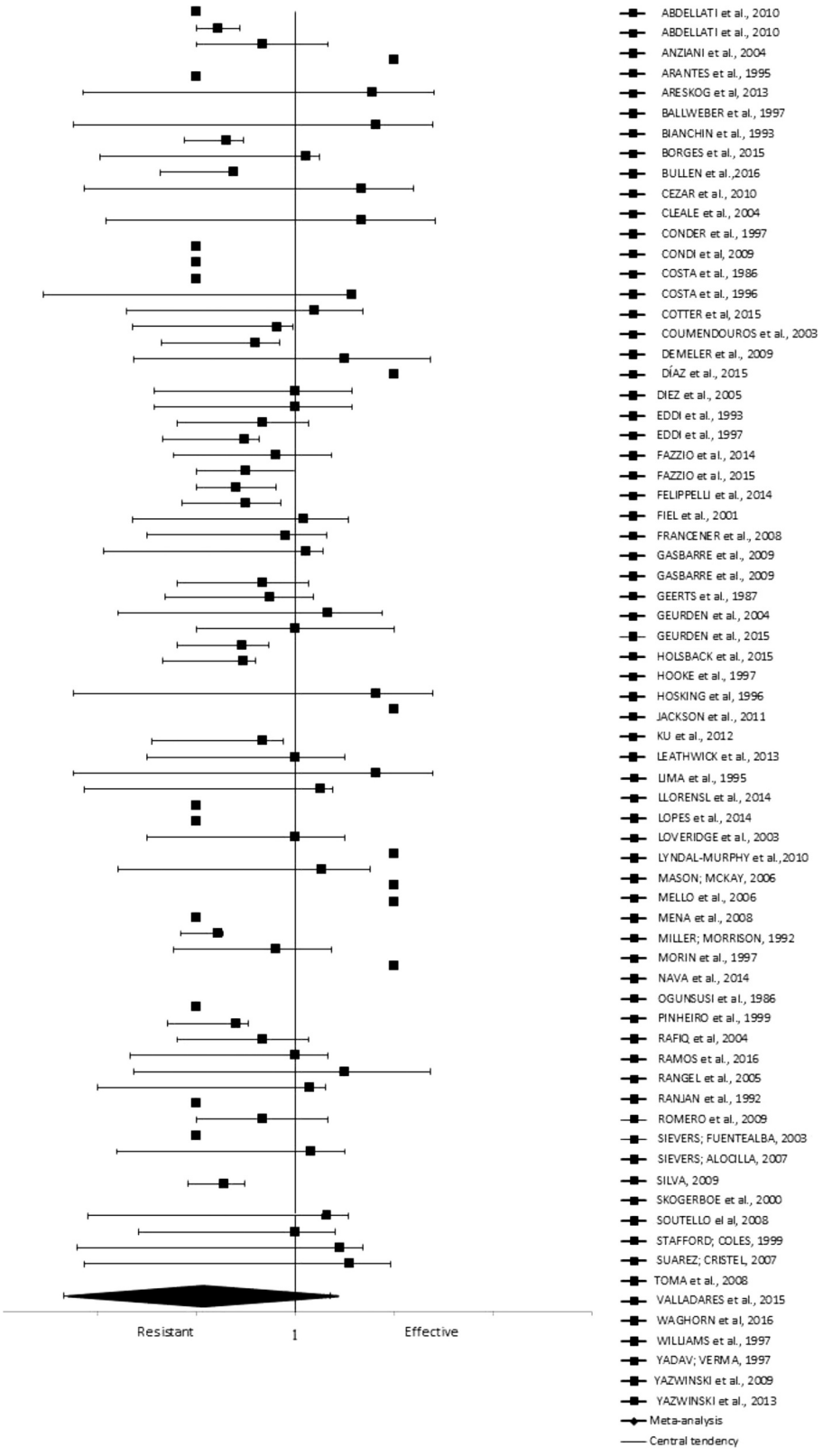

Fig. 1. Forest plot encompassing the seventy studies included in the meta-analysis of anthelmintic resistance of cattle infected by gastrointestinal nematodes. *I^2: 90%.

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