Macrocyclic lactones and ectoparasites control in livestock: Efficacy, drug resistance and therapeutic challenges

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ABSTRACT

Macrocyclic lactones (MLs) are the cornerstone of parasite control in livestock due to their broad-spectrum activity against endo (nematodes) and ecto (lice, ticks, mites) parasites. These molecules, introduced into the veterinary pharmaceutical market 40 years ago, have substantially improved animal welfare and productivity by offering extended high efficacy, reducing treatment frequency, and displaying a favorable safety profile. However, their widespread and intensive use has led to a significant challenge nowadays: *the development of parasite resistance*. This review focuses on the critical link between drug pharmacokinetics (variation in concentration profiles and exposure over time) and pharmacodynamics (drug efficacy) and the ability of both avermectin and milbemycin MLs families to control livestock ectoparasites. This review discusses the integrated assessment of drug behavior in the host, its diffusion into target parasites, and the impact of different pharmaceutical formulations on enhancing drug delivery to infection sites. These are considered critical research/development areas to optimize the use of MLs, preventing treatment failures and finally extending the lifespan of these essential pharmaceutical ingredients. Finally, the importance of the rational use of MLs, guided by parasite epidemiology and pharmacological knowledge, is emphasized as a key strategy to preserve the antiparasitic efficacy of these still very useful molecules.

1. Pharmacological basis of the broad-spectrum antiparasitic activity

The avermectins and milbemycins are closely related 16-membered macrocyclic lactones (MLs), produced through fermentation by soil dwelling actinomycetes (*Streptomyces*). The avermectin's family includes a series of natural and semisynthetic molecules, such as abamectin (ABM), ivermectin (IVM), doramectin (DRM) and eprinomectin (EPM). Nemadectin, moxidectin (MXD) and milbemycin 5-oxime belong to the milbemycin's family. Both families share some structural and physicochemical properties, and their broad-spectrum antiparasitic activity against nematodes and arthropods at extremely low dosage rates (Fig. 1). The unique ability of MLs to kill endo- and ectoparasites was what gave rise to the embracing name 'endectocide' by which the MLs are recognised (Shoop et al., 1995). A high affinity binding to glutamate-gated chloride channels, producing a slow and irreversible increase in membrane conductance, which paralyses the parasite somatic musculature, particularly, the pharyngeal pump (Geary et al., 1999), has been proposed as a main mode of action. The time of parasite exposure to active drug concentrations determines the efficacy and/or persistence of activity for MLs in ruminants (Lanusse and Prichard, 1993; Lifschitz et al., 2017).

IVM, DRM and MXD, currently marketed as injectable, pour-on (cattle) and oral (sheep, goats, pigs and horses) formulations, are most used MLs worldwide to control endo- and ectoparasites in livestock (McKellar and Gokbulut, 2012). EPM is a semisynthetic avermectin compound, developed originally for topical use in cattle (Shoop et al., 1996). The different MLs formulations available for livestock are shown in Table 1. High lipophilicity and the prolonged persistence of their potent broad-spectrum activity are distinctive features among antiparasitic drugs (see Fig. 1). Their spectrum and efficacy pattern are similar; however, each compound has its own dosage limiting species.

Differences in physicochemical properties among them may account for differences in formulation flexibility, kinetic behavior and in the potency/persistence of their endectocide activity. An enormous effort has been devoted to characterize the kinetics of the different MLs in different animal species. Plasma concentration profiles may help to predict the persistence of antiparasitic activity. However, measuring drug concentration profiles at the site of parasite location permits a more direct interpretation and provides a basis for understanding the differences in therapeutic and preventive efficacies observed for MLs. The extensive tissue distribution of MLs aligns with the large availability of these drugs in different parasite location tissues such as the gastrointestinal mucosal tissues, lungs and skin in cattle (Lifschitz et al., 1999a, 2000) (Fig. 1), where concentrations markedly greater than those observed in plasma were measured for 50–60 days post-treatment. The characterization of drug concentrations in target tissues may be useful to estimate the period post-treatment in which the endectocide levels at the site of parasite location remain efficacious. MLs endectocides are highly effective in eliminating ectoparasites after subcutaneous and topical administration. The pattern of MLs disposition in skin tissue showed that high concentrations are attained post subcutaneous treatment. The sustained presence of high concentrations of MLs in skin were reflected in the prolonged mean residence times values (between 6.8 and 9.3 days), which may also account for the efficacy of these drugs against ectoparasites (Lifschitz et al., 1999a, 2000). MLs concentration profiles in the skin (dermis and epidermis) were greater than those found in the hypodermal tissue (Lifschitz et al., 1999a, 2000). The dermis participates in the exchange of compounds between blood and tissues and as a fat reservoir (Monteiro-Riviere, 1991).

Ectoparasites controlled by MLs include mites (*Sarcoptes bovis, Psoroptes ovis*), oestrid larvae (*Hypoderma bovis, H. lineatum, Oestrus ovis*) and sucking lice (*Linognathus vituli, L. pedalis Haematopinus eurysternus)*. IVM, ABM and DRM are highly effective against *Dermatobia hominis* infestations (Vercruysse and Rew, 2002). While IVM and ABM aid in the control of the screw worm *Cochliomya hominivorax*, DRM has demonstrated a distinctive 100% protection for 21 days post-infection in calves (Moya-Borja et al., 1997). MLs are slightly less effective in controlling the sheep ked (*Melophagus ovinus)*. MLs are also highly effective against
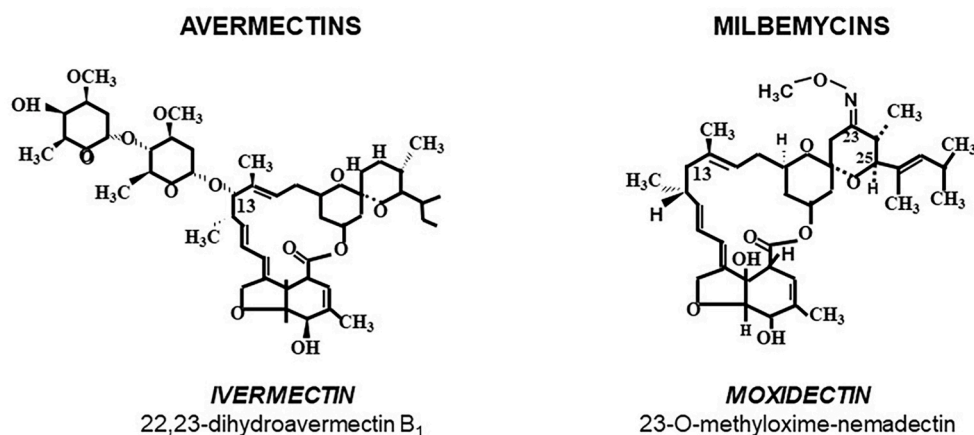
Table 1

List of macrocyclic lactone pharmaceutical formulations available as ectoparasiticides for use in cattle, sheep, pigs and horses.

Species	Formulation	Target ectoparasites
Cattle	Traditional 1% (0.2 mg/kg) and long-acting 3.15% (0.63 mg/kg) and 3.5 % (0.70 mg/kg) injectable solutions for subcutaneous administration. Applicable to IVM, DRM, MXD.	Ticks, psoroptic and sarcoptic mange, sucking lice.
	Pour-on 0.5 % solution (0.5 mg/kg) Applicable to IVM, DRM, MXD and EPN	Horn flies, sarcoptic and chorioptic mange, sucking and biting lices.
Sheep	Traditional 1% (0.2 mg/kg) and long-acting 3.15% and 3.5 % (1–1.2 mg/kg) injectable solutions for subcutaneous administration	Sheep scab[a] and itch mites
	Abamectin Pour-on 0.6 % solution (6 mg/kg)[1] Eprinomectin Pour-on 0.5 % solution (1 mg/kg)[2].	[1]Approved against *B. ovis* [2]Not approved for ectoparasites (used extralabel)
	Oral drench solution 0.08–0.1 % (0.2 mg/kg) Applicable to IVM and MXD	Not approved for ectoparasites
Pigs	Traditional 1% (0.3 mg/kg) injectable for subcutaneous administration. Applicable to IVM and DRM	Sarcoptic mange and sucking lice.
	Oral 0.6% powder premix (0.1 mg/kg over seven days)	Sarcoptic mange and sucking lice
Horses	Ivermectin 1,87% oral paste (0.2 mg/kg) and Moxidectin 2% oral gel (0.4 mg/kg)	Not approved for ectoparasites, extralabel use for sarcoptic mange (Osman et al., 2006).

[a] For sheep scab, the 1% formulation (IVM, DRM) should be administered twice with 7 days of interval.

cattle ticks (Davey and George, 2002; Davey et al., 2005).

The MLs endectocides contribute to the control of *Haematobia irritans* (horn fly) in cattle. These compounds kill the adult flies and inhibit larval development in cattle dung. Development of the *H. irritans* fly may be reduced over 4 weeks after treatment with some MLs compounds in

AVERMECTINS

MILBEMYCINS

IVERMECTIN
22,23-dihydroavermectin B$_1$

MOXIDECTIN
23-O-methyloxime-nemadectin

- 16-membered macrocyclic lactones
- Potent broad-spectrum ecto-endoparasitic activity
- Glutamate-mediated chloride increased conductance: paralysis+death in nematodes and arthropods
- High lipophilicity
- Slow disposition kinetics
- Sustained presence in target tissues
- Extended antiparasitic persistance

Fig. 1. Comparative chemical structures for both endectocide macrocyclic lactone families: avermectins and milbemycins. The main pharmacological features shared by compounds in both families are listed.

cattle (Marley et al., 1993). Besides, IVM appears as a multifaceted drug with a great potential beyond its antiparasitic activity (Kaur et al., 2024). IVM is currently been evaluated for its potential use in treating mosquito-borne parasitic infections (i.e. malaria). Additionally, IVM is now considered as a pleiotropic chemical agent with well-established antiviral, antiinflammatory and anticancer effects, becoming a model of a repurposing drug compound with impact both in human and animal health.

This review article contributes to understand the pharmacokinetic/pharmacodynamic relationship for the ectoparasitic activity of both the avermectin and milbemycin ML families. The epidemiological basis assisting the rational use of MLs in ecto-parasite control in livestock, integrated with an updated overview of their main pharmaco-therapeutic features is reviewed here.

2. Macrocyclic lactones to control cattle ticks: challenges to maintain their effectiveness

MLs have been used to control cattle ticks since IVM introduction into the market in 1981. Subcutaneous injections and topically applied pour-on formulations are used for controlling ticks (George et al., 2008). The efficacy of IVM delivered by orally administered bolus has also been tested to control cattle ticks (Soll et al., 1990; Miller et al., 2001), but it is not currently a commercially available option in most of the countries. Ticks are exposed to MLs during feeding over a period of several days; therefore, the frequency and duration of feeding may have a marked influence in drug uptake and efficacy (Jackson, 1989). The interruption of tick feeding caused by the paralysis on pharyngeal muscles by MLs results in lower females engorged weight, decrease in the reproductive capacity of females which is expressed as a reduction in both the number of eggs laid and egg hatchability. Besides, MLs produce a prolonged duration of feeding and a diminished rate of attachment with mortality of both adult and immature stages. In contrast to other drug families such as pyrethroids, organophosphates or amidines, there is no rapid and visible "knockdown" effect after MLs administration, which has been shown in a variety of studies (Nolan et al., 1981; Campbell and Benz, 1984; Jackson, 1989; Soll et al., 1990; Gonzales et al., 1993; Miller et al., 1997; Davey and George, 2002; George and Davey, 2004; Aguirre et al., 2005; Davey et al., 2005, 2010; Pereira, 2009; Lopes et al., 2013; Nava et al., 2019).

The main focus of the activity of MLs has been on boophilids (i.e., Rhipicephalus (Boophilus) microplus, Rhipicephalus (Boophilus) australis, Rhipicephalus (Boophilus) annulatus and Rhipicephalus (Boophilus) decoloratus), because these one-host ticks are the species group with the greatest health and economic relevance for cattle production systems in tropical and subtropical regions worldwide. The taxon named as R. microplus in studies from Australia corresponds in fact to R. australis (Guglielmone et al., 2023). All these trials have evaluated the effect of MLs on three main aspects on which the effectiveness of these drugs is measured: i) therapeutic efficacy based on tick reduction in treated animals in relation to a control group through the count of tick number attached to treated hosts (i.e. unengorged, semiengorged (usually in one-host ticks) and engorged females; immatures stages; males); ii) determination of the residual protection (persistent efficacy) period against post-treatment larval re-infestation of one-host ticks (boophilids), where the number of engorged females that developed from each larvae exposition is evaluated; iii) effect on the reproductive capacity of the females (expressed as engorgement weight, number of eggs laid by females, and egg hatching percentage), and on the molting success of engorged immature stages in the case of multi-host ticks. Therefore, the comparative assessment of the activity of MLs against ticks reported in experimental studies based on artificial tick challenge and in field trials with natural infestation should be done by separately considering the different parameters by which the effectiveness of these drugs is measured. It should also be noted that the susceptibility of the tick strain may influence on the efficacy result in those trials performed under field conditions with natural tick infestation.

Most studies on the efficacy of MLs against three-host ticks involve IVM applied at different dosages and administration routes (Miller et al., 1997; Campbell and Benz, 1984; Lancaster et al., 1982). In all cases, the effect of MLs on Amblyomma infestation in cattle was far from absolute control, with numerous specimens remaining attached to the hosts, although many of them were biologically non-viable. Achieving sustained control of Amblyomma infestations on cattle under field conditions, within the framework of an annual plan, can be complex. First, species of this genus use cattle as an alternative host, and part of the population can feed on wild mammals, limiting widespread exposure to the drug and reducing its impact on population abundance. Second, the sequential seasonal activity of each parasitic stage throughout the year, characteristic of some Amblyomma species whose immature and adult stages parasitize cattle, necessitates a series of repeated drug treatments, which could lack sustainability and become impracticable. Similar effects to those reported for Amblyomma were observed in other multi-host species such as R. evertsi, R. appendiculatus, H. anatolicum, and H. marginatum when cattle were treated with IVM orally or parenterally. Reduction in the reproductive capacity of females, prolonged engorgement, and reduction in the total number of ticks recovered were some of the parameters affected in these tick species (Campbell and Benz, 1984; Soll et al., 1990). Among argasid ticks, Otobius megnini (Argasidae) is one of the most significant cattle parasites worldwide. Larvae and nymphs (adults are free-living) of this species usually feed deep in the external ear canal of cattle. Facchin et al. (1998), and Nava and Guglielmone (2009) reported the failure of MLs to control infestations with larvae and nymphs of this tick species in cattle. Nava and Guglielmone (2009) also reported the failure of EPM pour-on to impair nymphal molting capacity and conjectured that the lack of efficacy of MLs to control O. megnini nymphal infestation is likely connected to the lengthy and slow feeding process of this tick species.

Undoubtedly the use of MLs is mainly focused to the control of one-host ticks, namely R. microplus, R. australis and R. annulatus. A representative summary of the results obtained in experimental and field studies on the efficacy of MLs to control R. microplus on cattle is presented in Table 2. A similar spectrum of action was observed when MLs were tested with R. australis, R. annulatus and R. decoloratus (Nolan et al., 1981; Soll et al., 1990; Remington et al., 1997; Miller et al., 1999, 2001; El-Bahy et al., 2015). Overall, injectable formulations perform better (efficacy and persistence) than those of topical administration. This can be attributable to the fact that injectable formulations lead to a better systemic exposure (bioavailability) than pour-on formulations, as shown for MXD in cattle by Sallovitz et al. (2003). However, the immunological status of the herd with respect to iatrogenic borne haemoparasites and the risk of anaplasmosis outbreak at the time of treatment are aspects to consider before applying an injectable drug to control cattle ticks (George et al., 2008). Some formulations allowed absolute control, but this is not immediate in the first days after treatment. In addition to the absence of a "knock-down" effect, MLs are less effective against engorged females at the final stages of development, which can produce viable larvae (Nolan et al., 1981; Davey and George, 2002; Davey et al., 2007; Lifschitz et al., 2016; Nava et al., 2019). The reason is the presence of a lag phase immediately after treatment, during which the ticks do not receive a lethal dose of the drug because the concentration of MLs in the bloodstream has not yet reached effective levels. The high levels of efficacy (e.g., 99%) could be expected when the drug reaches a threshold concentration of > 8 ppb (Davey et al., 2010, 2011, 2012). An accumulation of ticks attached to treated hosts has also been observed, related to the fact that tick development is affected by the treatment but not enough to die and detach immediately. Observations in field trials evidenced that some immature ticks fed on cattle treated with IVM tend to survive to the young adult stage before succumbing to the treatment (Nolan et al., 1981; Nava et al., 2019). Therefore, MLs should be used with knowledge of these aspects when they are applied to eradication plans or in treatments when cattle *move from tick-infested* areas into

Table 2
Representative summary of the results obtained in different studies on the efficacy of a single treatment with macrocyclic lactones to control *Rhipicephalus microplus* ticks on cattle. DPT: Days post-treatment with efficacy greater than 90%. FRP: Reproductive parameters of females. ET: Experimental trial with artificial infestation. FT: Field trial with natural infestation.

Drug and type of trial	DPT with efficacy [a] > 90%	Effect on FRP	Reference
Ivermectin (200 μg/kg injectable): ET	28	Yes	Cramer et al. (1988a)
Ivermectin (200 μg/kg *pour on*): ET	No	Yes	Cramer et al. (1988b)
Ivermectin (500 μg/kg *pour on*): ET	No	Yes	Cramer et al. (1988b)
Ivermectin (200 μg/kg injectable): FT	12–28[c]	–	Caproni et al. (1998)
Ivermectin (200 μg/kg injectable): ET	19	Yes	Bulman et al. (2000)
Ivermectin (500 μg/kg *pour on*): ET	No	Yes	Davey and George (2002)
Ivermectin (200 μg/kg injectable): ET	7	Yes	Davey et al. (2005)
Ivermectin (200 μg/kg injectable): ET	no	Yes	Pereira (2009)
Ivermectin (630 μg/kg injectable): FT	56[c]	–	Arieta-Román et al. (2010)
Ivermectin (630 μg/kg injectable): ET	14	Yes	Davey et al. (2010)
Ivermectin (630 μg/kg injectable): FT	15[c]	Yes	Lopes et al. (2013)
Ivermectin (630 μg/kg injectable): FT[b]	49[c]	–	Cruz et al. (2015)
Ivermectin (630 μg/kg injectable): ET	21	Yes	Cuore et al. (2016)
Ivermectin (630 μg/kg injectable): FT	21[c]	Yes	Nava et al. (2019)
Doramectin (200 μg/kg injectable): ET	21	Yes	Gonzales et al. (1993)
Doramectin (200 μg/kg injectable): FT	8–28[c]	–	Muñiz et al. (1995)
Doramectin (200 μg/kg injectable): FT	28[c]	–	Caproni et al. (1998)
Doramectin (200 μg/kg injectable): ET	21	Yes	George and Davey (2004)
Doramectin (500 μg/kg *pour-on*): ET	No	Yes	George and Davey (2004)
Doramectin (200 μg/kg injectable): ET	28	Yes	Pereira (2009)
Doramectin (700 μg/kg injectable): FT	40[c]	Yes	Lopes et al. (2013)
Moxidectin (500 μg/kg *pour-on*): ET	No	Yes	Davey and George (2002)
Moxidectin (200 μg/kg injectable): FT	7–28[c]	–	Aguilar-Tipacamu and Rodriguez-Vivas (2003)
Moxidectin (200 μg/kg injectable): ET	7	Yes	Davey et al. (2005)
Moxidectin (1000 μg/kg injectable): FT	70[c]	–	Arieta-Román et al. (2010)
Moxidectin (1000 μg/kg injectable): ET	42	Yes	Davey et al. (2011)
Moxidectin (1000 μg/kg injectable): FT	40[c]	Yes	Lopes et al. (2013)
Eprinomectin (500 μg/kg *pour-on*): ET	No	Yes	Davey and George (2002)
Eprinomectin (500 μg/kg *pour-on*) ET	28	Yes	Aguirre et al. (2005)
Eprinomectin (1000 μg/kg *pour-on*) FT	23[c]	Yes	Lifschitz et al. (2016)
Eprinomectin (200 μg/kg injectable) FT	5–23[c]	Yes	do Nascimento et al. (2020)
Abamectin (200 μg/kg injectable) ET	No[d]	Yes	Bridi et al. (1992)
Abamectin (200 μg/kg injectable) ET	No	Yes	Pereira (2009)

[a] The formulae and parameters used to calculate the efficacy are different between experimental and field studies. Briefly, the efficacy calculated in experimental studies is based on the effect of a drug to preclude the development of larvae into engorged females, and to inhibit the reproductive capacity of females. The number of days expresses the protective period against larval reinfestation. The therapeutic efficacy used to evaluate a treatment under field conditions refers to the reduction in the number of attached ticks (usually semi-engorged females) in treated animals in relation to a control group. There are also differences in susceptibility to the drugs among tick strains subjected of the treatments. Therefore, values are not strictly comparable.

[b] Cruz et al. (2015) treated field populations of *R. microplus* with other injectable (200 μg/kg) and oral (500 μg/kg) formulations of ivermectin, but they were classified as resistant. Therefore, data corresponding to resistant tick populations were not included in this table.

[c] The values in field tests refer to the days when values of efficacy >90% were reached.

[d] Bridi et al. (1992) also test treatments of injectable abamectin at 100 μg/kg and 300 μg/kg, ante the results were not significantly different to those obtained at 200 μg/kg.

tick-free areas. Currently, the use of MLs against cattle ticks faces important constraints as the development of parasite resistance, the nontarget effect in the environment by residues in the dung of treated animals, and the accumulation of chemical residues in meat or milk imposed by the long withdrawal periods of long-acting formulations.

Resistance to antiparasitic drugs is one of the main limitations for chemical control, which becomes difficult to manage once it has been developed in a farm. With the only exception of fluralaner (at least at the date when this article was written), cases of resistance of boophilids to all commercially available chemical acaricides have already been detected in different continents, and this also include some tick populations with multi-resistance. Regarding MLs, there are reports of resistance of *R. microplus* to DRM, MXD, and EPM (Martins and Furlong, 2001; Ferreira et al., 2022). However, most resistance records are for IVM, which is not surprising given its long-standing predominance in commercial ML formulations for cattle tick control. Cases of resistance of *R. microplus* to IVM were recorded in different American countries such as Argentina, Brazil, Colombia, Ecuador, Mexico, Uruguay (Martins and Furlong, 2001; Perez-Cogollo et al., 2010; Castro-Janer et al., 2011; Fernandez-Salas et al., 2012; Klafke et al., 2012; Rodriguez-Vivas et al., 2014; Cuore et al., 2017; Klafke et al., 2017; Rodriguez-Hidalgo et al., 2017; Chaparro-Gutiérrez et al., 2020; Torrents et al., 2020). There are also reports of resistance of *R. microplus* and *R. annulatus* to IVM in India and Egypt, respectively (El-Ashram et al., 2019; Fular et al., 2021; Nazim et al., 2022). The widespread use of IVM to control *R. microplus* can also increase the selection pressure on other MLs, even in the absence of prior use. Martins and Furlong (2001) reported cross-resistance of *R. microplus* between DRM, MXD and and Ferreira et al. (2022) found that resistance to MXD and EPM may occur because of continuous high selection pressure by the sole use of IVM. Moreover, the treatment of cattle with IVM for the control of gastrointestinal nematodes promoted simultaneously the development of IVM resistance in gastrointestinal parasites and in *R. microplus* ticks in the same cattle herd (Alegría-López et al., 2015).

The development of different formulations based on the combination of avermectins with other chemical groups for use against *R. microplus* should also be carefully considered. There are mixtures of IVM + fluazuron, ABM + fluazuron, IVM + ABM, EPM + novalurom, IVM + fipronil, among others (Borges et al., 2008; Alves-Branco et al., 2010; Cruz et al., 2014; Costa-Gomes et al., 2015; Maciel et al., 2016; Robaina et al., 2021; Sarli et al., 2023). Combinations of drugs may delay or mitigate the onset of resistance under the following conditions: i) resistance to each active compound is controlled by a single gene and is genetically independent, ii) resistance genes are recessive, iii) individuals with multiple resistances are rare, and iv) the drugs in the combination have similar persistence (Curtis, 1985; Tabashnik, 1989; Cloyd, 2010). Unfortunately, these assumptions are not always fulfilled. A rapid increase in resistance to multiple chemical groups may occur if individuals possess mechanisms of multiple resistance or if the use of

combinations amplifies selection pressure by promoting the expression of metabolic enzymes capable of detoxifying multiple compounds (Tabashnik, 1989; Cloyd, 2010). The most problematic consequence of acaricide resistance development is the selection of tick populations with multi-resistance (Fernandez-Salas et al., 2012; Cuore et al., 2017; Klafke et al., 2017). Successive applications of a drug mixture can result in the simultaneous rise of resistance to both drugs, as demonstrated by Sarli et al. (2023) for a combination of IVM and fipronil.

Detecting resistant populations is essential for the effective use and management of MLs in tick control. Bioassays for detecting resistance to MLs are commonly used, with the larval immersion test being one of the most sensitive *in vitro* assays for differentiating between resistant and susceptible *R. microplus* populations to IVM (Castro-Janer et al., 2011; Fernandez-Salas et al., 2012; Klafke et al., 2012, 2017; Chaparro-Gutiérrez et al., 2020; Torrents et al., 2020). However, *in vitro* tests have significant limitations, including a time delay of approximately 45 days from tick sample submission to result acquisition and the inability to detect resistant genotypes that have not yet reached a high enough frequency to be expressed at the population level. Molecular diagnostic tests could potentially address these issues. ATP-binding cassette (ABC) transporters are the primary mechanisms involved in the detoxification of IVM in *R. microplus*, with enzyme families such as cytochrome P450, glutathione-S-transferases, and esterases may also contributing to drug clearance (Pohl et al., 2011; Le Gall et al., 2018). However, the molecular basis of tick resistance to MLs is not yet fully understood, and practical molecular diagnostic methods are currently unavailable.

The second step for MLs management is to design treatment schemes that allow acceptable tick control but preserve the functionality of the endectocide drugs. Prevent long exposure periods of a tick population to the same chemical group is one approach in this direction. Rotational treatments using two or more active ingredients with different modes of action have been proposed to reduce selection pressure and the odds of potential for cross-resistance (Thullner et al., 2007; Jonsson et al., 2010; Rodríguez-Vivas et al., 2017). The strategic and generational control schemes for *R. microplus*, designed for use in subtropical regions, aim to reduce the annual frequency of treatments by employing a sequence of applications that alternate chemical groups with different active ingredients and modes of action (Cuore et al., 2013; Nava et al., 2020, 2021). In these therapeutic schemes, the same chemical group is not used more than once or twice a year. The biological basis for alternating treatments lies in understanding that the off-host tick population in a paddock consists of three groups: detached engorged females, eggs, and free-living larvae. During the persistence period of MLs, only the questing larvae are exposed to the treatment, while detached engorged females, eggs, and non-questing larvae remain untreated. This untreated portion of the tick population is referred to as the "refuge." The concept of refuge represents the segment of the parasite population that is not subjected to the selection pressure of the drug (Hodgkinson et al., 2019). The more successive treatments with the same drug, the smaller the refuge for that drug. The perceived value of persistence in long-acting ML formulations should be balanced against the selection pressure for resistance due to declining concentrations of residual acaricide (George et al., 2008). Successive applications of long-acting formulations of avermectins, which are quite for *R. microplus* control, can significantly reduce the refuge in the pasture and increase the selection pressure for resistance. In that regard, Sarli et al. (2022, 2023) have found a noticeable increase in resistance ratios after the application of three successive treatments with IVM 3.15% every $\approx$ 35–40 days. Occasionally tactical treatments are also needed as a complement to those carried out within the strategic or generational plan when large tick burdens are higher than expected. These tactical treatments should be applied only to heavily infested herds, preserving a refugia of untreated animals. Another aspect to consider is that long-acting IVM have a concentration–time curve where the values after $\approx$40 days post-treatment are below the threshold dose (8 ppb) expected to be effective against *R. microplus* (Lifschitz et al., 2007; Davey et al., 2010). Because of this

pharmacokinetic-related feature, a fraction of the tick population could be exposed to subtherapeutic doses of the drug. Therefore, it would be prudent not to use long-acting avermectins as the final therapeutic option in a sequence of treatments that involve rotating chemical groups with different modes of action. Rotational strategies involve using MLs that, despite some level of resistance, still offer acceptable control against ticks.

To improve control of resistant ticks, developing formulations MLs with chemical synergists (Khangemban et al., 2018; Shakya et al., 2022) or combining MLs with anti-tick vaccines (Arocho-Rosario et al., 2022) could be viable options. Another approach is integrated tick control, which combines different tools where only one involves chemical use. This approach includes synthetic acaricides, pasture management (like resting periods), and breeding tick-resistant cattle (*Bos indicus* breeds). While biological control and non-synthetic acaricides (e.g., essential oils) exist, they are not currently practical for controlling high tick infestations in cattle. Extending the successful use of MLs in tick control remains a significant challenge. However, achieving this goal demands a comprehensive, multidisciplinary approach that addresses various critical pharmacological and parasitological aspects.

3. Macrocyclic lactones and mange control: the silent resurgence of an ancient adversary

3.1. Cattle mange

Most of the roughly 1.49 billion cattle worldwide are at risk of being infested by different ectoparasites. Mites are particularly noteworthy among these parasites, as they have a significant economic impact due to the direct consequences of heavy infestations on animal health and food production (Pérez de León et al., 2020). The presence of psoroptic mange may increase the maintenance energy requirements of calves, even when *P. ovis* infestations are low (Cole and Guillot, 1987). Besides, when infestations cover 30 % of the body area an important reduction in daily weight gain was measured (Cole et al., 1984). Different mites are responsible for varying forms of mange. Cattle are mainly affected by three types of mange according to the mite species causing it: sarcoptic mange (*Sarcoptes scabiei*), chorioptic mange (*Chorioptes bovis*) and psoroptic mange (*Psoroptes ovis*). Sarcoptic and psoroptic mange mainly affect growing cattle, and infestation may result in severe disease, while infestation with *Chorioptes* mites is predominately found in dairy cattle and less often reported as the cause of an extended dermatitis. Mange control has been based on the use of acaricidal dips. However, the pharmacological characteristics of the MLs such as its potency lipophilicity and high distribution to the skin layers imposed its massive use in the treatment of cattle mange (Meleney, 1982; Campbell and Benz, 1984; Lifschitz et al., 2000).

Psoroptes ovis, a nonburrowing mite, causes psoroptic mange by puncturing the skin to feed on wound exudates, potentially resulting in the formation of a thick crust. This condition is marked by exudative dermatitis, alopecia, and severe itching, posing a lethal threat to untreated calves (Fisher and Wright, 1981; Pérez de León et al., 2020). The disease frequently follows a severe clinical course and may lead to important losses from mortality and impaired productivity (Eddi et al., 2002). Since 1980, IVM has been considered one of the most effective treatments against psoroptic mange (Campbell, 2012). Although mite eggs are not susceptible to this drug, the persistence of IVM in the animals leads to the death of newly born larvae and the elimination of the *P. ovis* infestation following a single injection of 0.2 mg/kg (Guillot and Meleney, 1982; Lonneux et al., 1997).

Beyond the differences among MLs, both IVM and DRM showed 100 % efficacy against *P. ovis* after their launch on the veterinary pharmaceutical market (Meleney, 1982). The intensive use of IVM during the last 40 years reduced extensively the number of mange outbreaks in endemic regions. But also, using parasiticides in this intensive way has not been sustainable because it has led to the emergence of the first

reports on IVM failure. The international guidelines supplied by the World Association for the Advancement of Veterinary Parasitology (WAAVP) establish that the criterion for efficacy is to achieve statistically significant ($P < 0.05$) differences in mite counts between treated and untreated control groups, and ≥ 90 % efficacy (Vercruysse et al., 2006; Holdsworth et al., 2022). Field reports on failure of IVM in the treatment of cattle mange have increased in recent years in some countries such as Argentina, both in feedlot (Lifschitz et al., 2018) and in grazing systems (Canton et al., 2023), and Belgium (Lekimme et al., 2010; Van Mol et al., 2020). In this context, the identification of different factors that can affect the pharmacokinetic/pharmacodynamic relationship on the action of MLs against *P. ovis* is relevant to extend their lifespan as useful tools for mange control. For example, it was corroborated a positive correlation between plasma and skin concentrations of IVM subcutaneous administered to healthy animals and to cattle affected by mange (Lifschitz et al., 2000, 2018). The ratio skin-/plasma availability in the animals affected by mange were in the same range than those observed in healthy calves (Lifschitz et al., 2000, 2018). Fig. 2 shows the correlation between plasma and skin IVM concentrations. Another relevant issue is that differences in physicochemical properties among MLs may account for differences in their disposition kinetic and in their antiparasitic activity (Lanusse et al., 1997). For example, plasma and skin availability of DRM were 1.6–1.9 greater than those measured after IVM administration to cattle (Lifschitz et al., 2000). Therefore, Canton et al. (2023) evaluated if this kinetic disposition difference may impact on the efficacy against cattle mange with reduced susceptibility to MLs in Argentina. They demonstrated that although the reduction in mites' susceptibility to both MLs was evident, the performance observed after the administration of DRM 1 % was significantly greater compared to IVM 1 %. Whereas DRM 1 % cured 80 % of the treated animals on day 14, the percentage of cured animals was only 10 % for the IVM 1 % group. The better performance of DRM 1 % treatment *in vivo* may be based on the greater systemic exposure compared to IVM. Thus, the ratio between systemic drug exposure and mite exposure as a PK/PD biomarker was greater for DRM 1 % compared to IVM 1 %. The divergence in drug effectiveness was clearly demonstrated in their effects on cattle productivity. Following treatment, cattle treated with DRM showed a notably higher average weight gain compared to those treated with IVM, indicating the superior performance of the former medication (Canton et al., 2023). Despite these differences, both drugs failed to achieve cure in 100 % of animals, showing a reduction in mite susceptibility to both molecules. Similar results were observed in several farms in Belgium in which between 2 and 7 rounds of treatment using different MLs were necessary to achieve the parasitological cure of 100 % of the affected animals (Van Mol et al., 2020).

After the launch of the pioneer preparation of IVM formulation at 1 %, different pharmaceutical formulations have been introduced to extend the IVM persistent endectocide activity in cattle. Highly concentrated (3.15–3.5 %) long-acting preparations are administered to cattle at 630–700 µg/kg dose. The vehicle properties of the long-acting formulations favor a slow absorption from the subcutaneous site and prolong the persistence of IVM concentrations in the bloodstream, and in the tissues of parasites location (Lifschitz et al., 2007). As it was observed for ticks, drug exposure following IVM injection occurs during mite feeding (Jackson, 1989). The IVM long-acting formulation has shown a high efficacy against psoroptic mange (Hamel et al., 2015). In a context of reduced susceptibility in mites, it is emphasized the importance of the level and the length of drug exposure for obtaining an optimal efficacy against *P. ovis*. Although the systemic exposure to IVM was 3.37-fold higher with the long-acting formulation compared to the traditional 1 %, the prolonged levels of IVM in the bloodstream achieved with the 3.15 % formulation were insufficient to achieve 100 % efficacy on a grazing cattle farm in Argentina (Table 2). This outcome suggests a rightward shift in the dose-response curve of IVM against mites, resulting in reduced effectiveness even at higher drug exposure (Canton et al., 2023).

Fortunately, not all farms face this situation. On another commercial cattle farm in Argentina, Canton et al. (2023) reported a parasitological cure in 100 % of animals on day 21 (IVM 3.15 %) and 28 (DRM 3.5 %) suggesting a higher susceptibility of the mite population to these formulations. Indeed, the ratio AUC plasma/AUC mites, used as a PK/PD biomarker, was significantly higher with the long-acting formulations compared to traditional 1 % preparations. The extended time to reach 100 % efficacy between 21 and 28 days post-treatment may be attributed to slow absorption of these preparations or potentially indicate reduced mite susceptibility to the drugs. This delayed efficacy has practical implications such as the need for extended quarantine periods following routine treatments.

Sarcoptic mange, caused by *S. scabiei* var. *bovis*, a skin-burrowing mite that lives in the epidermis of their host, is highly contagious and zoonotic skin disease characterized by inflammation, intense itching, hair loss, and skin thickening. In contrast, chorioptic mange, caused by *C. bovis*, is typically milder and superficial affecting mainly in milking-age cows (Rehbein et al., 2005a). Rehbein et al. (2003) reported that the mixed *Sarcoptes/Chorioptes* mite infestation of bulls not only affected the liveweight gain and feed conversion efficiency but also caused deleterious effects on the value of the carcasses which represents the main income of the producer. In that study, the successful treatment with injectable IVM lead to a remarkable recovery in productivity. Unlike psoroptic mange, a topically administered IVM demonstrated that was fully effective against *C. bovis* and *S. scabiei* var bovis on cattle
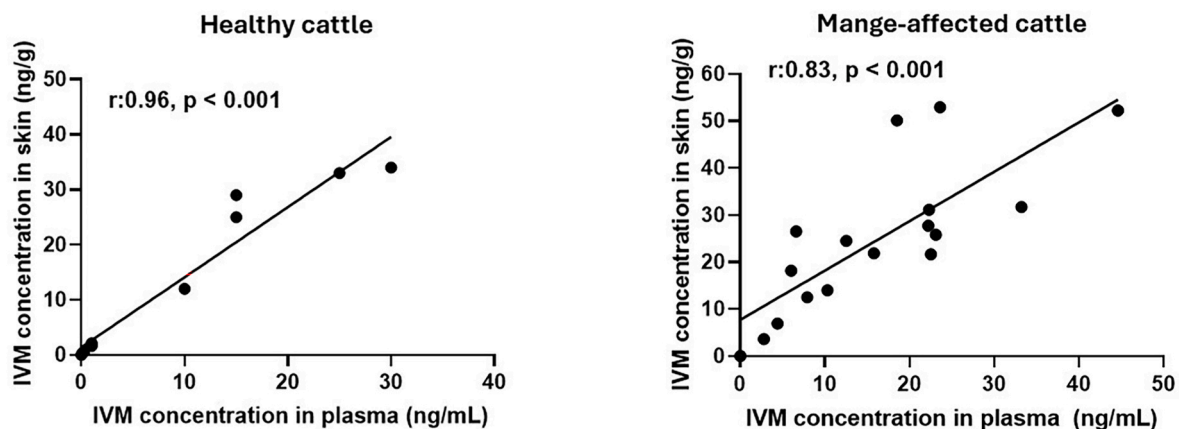

Fig. 2. Relationship between plasma and skin ivermectin (IVM) concentration profiles measured in healthy and *Psoroptic spp.* infected cattle: correlation between IVM concentrations in the bloodstream and skin tissue. Adapted from Lifschitz et al. (2000, 2018).

(Barth and Preston, 1988). Similarly, one topical application of MXD (Losson and Lonneux, 1996) or DRM (Rooney et al., 1999) was highly efficacious against chorioptic and sarcoptic mange in naturally infected cattle. Considering chorioptic mange is typically observed in dairy cattle, Rehbein et al. (2005a) confirmed the efficacy of topical EPM against naturally acquired *C. bovis* mite infestations in this category. Mite counts for the cattle treated with EPM were reduced by 100% from day 14 through the end of the study. Furthermore, these findings are supported by the weight gain differences observed by Barth et al. (1997) after treatment with topical EPM to dairy cattle. All these results are relevant considering that EPM is one of the only parasiticide approved for use in dairy herds, without requiring withdrawal times for milk. A field study evaluated the effects of an entire herd treatment with topical EPM on natural occurring chorioptic mange lesions on a commercial dairy farm under typical field conditions. The results of this study showed that chorioptic mange can be controlled in entire herds, although multiple treatments will be required to potentially eradicate the parasite. The value of the study is that it shows that mange can be controlled in dairy cattle with approved drugs, eliminating the need to use non-approved agents (Villarroel and Halliburton, 2013). Further studies support the efficacy of extended-release formulations of EPM for treating bovine sarcoptic mange, demonstrating its effectiveness (Visser et al., 2013). All these findings underscore the economic significance of managing both chorioptic and sarcoptic mange in cattle and emphasize the role of MLs in controlling these parasitic infections effectively.

In conclusion, mite infestations significantly impair cattle productivity and, in severe cases, can lead to mortality, causing substantial economic losses for cattle producers globally (Pérez de León et al., 2020). Therefore, effective mange control is crucial to maintaining adequate production levels on commercial cattle farms. The use of MLs for mange control should be carefully evaluated for each individual cattle farm, particularly considering the treatment failures that are often reported for psoroptic mange. Early identification and diagnosis are critical to improving treatment outcomes. In addition to management practices like quarantine, maintaining environmental cleanliness, rotating pastures, coordinating treatments with neighboring farms, and regular veterinary monitoring are essential for preventing the spread of mites and reducing infestation risks. These integrated approaches are crucial for successfully managing and containing mange outbreaks in cattle.

3.2. Sheep scab

Psoroptic mange (commonly known as sheep scab) is one of the most important ectoparasitic diseases of sheep. Clinical manifestations are progressive and, during the early stages of infestation, the animals could be asymptomatic (Bates, 1997). As the disease progresses, clinical manifestations of sheep scab include intense pruritus, alopecia, erythema, crusting, and thickening of the skin. Psoroptic mange is currently addressed using three types of chemical compounds: MLs administered through subcutaneous injections, organophosphates and pyrethroids for total-immersion plunge dips (Larroza et al., 2020a).

The use of MLs has been successful for many years in managing and preventing sheep scab outbreaks, contributing to improved animal welfare and sustained productivity in the sheep farming industry. Pharmacokinetic differences between ruminant species significantly impact MLs efficacy against scabies mites. For instance, IVM exhibits higher plasma levels in cattle compared to sheep and showed a 93 % greater systemic availability in cattle after its subcutaneous administration (Lifschitz et al., 2007; Lloberas et al., 2012). Fig. 3 shows the comparison of the plasma kinetic profiles after the subcutaneous administration of IVM 1 % to both ruminant species. Consequently, traditional 1 % formulations of MLs often require two administrations at 7-day intervals in sheep, while a single administration meet the requirements in cattle for psoroptic mange treatment. With the advent of long-acting formulations, a single dose can now effectively control sheep
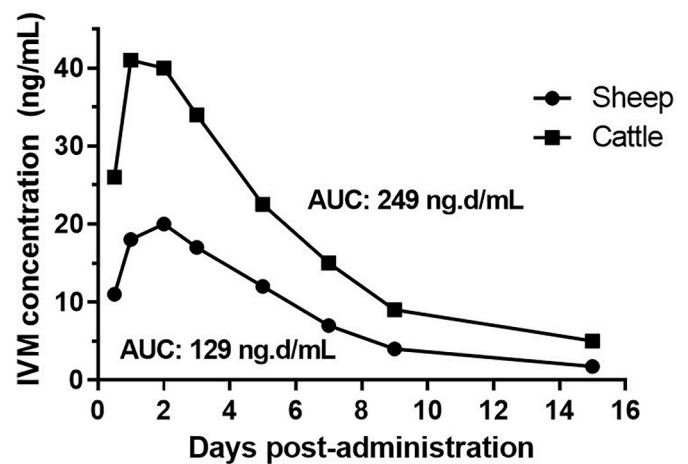

Fig. 3. Comparative ivermectin (IVM) plasma concentration profiles after its subcutaneous administration to sheep and cattle at 0.2 mg/kg. The systemic availability (drug exposure) expressed as AUC is shown. Adapted from Lifschitz et al. (2007) and Lloberas et al. (2012).

scab in countries where these formulations are available.

After many years of high efficacy, the appearance of resistance of P. ovis to MLs has been demonstrated. Doherty et al. (2018) confirmed the resistance to these compounds *in vitro*, using mites from sheep farms with a history of treatment failures. These mites survived exposure to MXD concentrations between 500 and 2000 ng/mL, while mites from farms without MLs use did not. Subsequently, Sturgess-Osbone et al. (2019) evaluated the *in vitro* efficacy of IVM, MXD, and DRM against P. ovis from similar sheep farms with treatment failures. Their study revealed resistance to all three MLs in some of the mite populations. Similarly in Argentina, veterinarians have empirically observed the failure of MLs, mainly IVM and DRM, when these compounds were used to control psoroptic mange outbreaks in different areas of this country. A recent study by Soler et al. (2022) identified *in vitro* resistance to IVM and a trend of cross-resistance to DRM. However, the study also highlighted that MXD demonstrated greater efficacy against mites compared to IVM. While these findings are encouraging, field trials are necessary to validate the greater effectiveness of MXD. The performance of each ML can vary depending on the farm. Generalizing findings from one location may not accurately reflect results in other areas. Therefore, the evaluation of the efficacy of each ML by practitioners is relevant for a rational use of these antiparasitic compounds.

In this context, different pharmacological strategies were addressed to evaluate the effectiveness of different formulations of MLs and to compare the efficacy among the different MLs within a context of resistance. *In vivo* trials using lambs infected with mites resistant to traditional IVM treatment (1 % formulation on days 0 and 7) corroborated its limited efficacy (Larroza et al., 2020a). While the traditional treatment reduced the mite counts by 83 % on day 14 and achieved a maximum efficacy of 93 % by day 28, it failed in the mange complete eradication showing the emergence of field mite populations with reduced susceptibility to IVM. The choice of formulation can significantly impact treatment success. However, even with a long-acting formulation, complete elimination of mites remains elusive. Larroza et al. (2020a) observed a 150 % increase in systemic availability and a five-fold longer elimination half-life compared to the traditional 1 % injectable formulation. Despite this improved drug exposure, the maximum efficacy achieved was 95.9 % at 21 days post-treatment. These results highlight the necessity for alternative treatment strategies. As it was observed in cattle, a superior performance of DRM compared to IVM was obtained against mites with reduced susceptibility in sheep. Treatment with two doses of 1 % DRM resulted in a significant decrease in mite counts by day 7, reaching a peak efficacy of 98.8 % by

day 28. A single dose of the long-acting DRM formulation also showed significant reductions in mite counts, achieving complete parasitological cure (100 % efficacy) by day 35 (Larroza et al., 2020b). In countries such as Argentina, ovine psoroptic scabies is a notifiable disease, and the National Service of Animal Health (SENASA) requires a 100 % treatment efficacy by day 14 or 21 post-treatment for commercially available sheep scab control products. The fact that DRM 1 % did not achieve 100 % efficacy while the long-acting DRM formulation (3.15 %) reached 100 % efficacy by day 35 post-treatment (Larroza et al., 2020b) suggests a potential decrease in efficacy compared to the results obtained during official regulatory testing prior to market launch.

While the treatments with MLs did not achieve the required acaricidal effect to cure the animals, the significant decrease in the mite populations led to an improvement in the condition of the sheep and a decrease in itching after the first week of treatment (Larroza et al., 2020b). In the field, when producers observe this picture, they may mistakenly interpret that the treatments were effective, even though the time required to achieve effectiveness was longer than expected, for example after the administration of long-acting formulations. Animals that have not achieved parasitological cure and still have live mites may be the source of new contagion for the rest of the flock. In this context, the reappearances of outbreaks observed in affected flocks, are attributed both to failures in the treatments and to management problems, such as inadequate gatherings where not all animals are treated, incorrect dosages, failures in the equipment, poor condition of fences that allow contagion between farms (Larroza et al., 2020a). The primary focus for sheep scab control is on prevention, specifically by implementing strict biosecurity measures, with a key emphasis on quarantining all incoming animals to a farm (Busin, 2018). An illustrative summary of the *in vitro* and *in vivo* studies that revealed either resistance or at least a lack of efficacy against *P. ovis* in sheep and cattle is provided in Table 3.

3.3. Pigs and horses mange

Sarcoptic mange infestation in pigs is caused by the mite *S. scabiei* var. suis, which leads to significant morbidity in farm animals (Laha, 2015). These parasites penetrate deep into the skin, causing itching sensations, stress, and resulting in the loss of body weight in infested pigs. This can lead to decreased growth rates, fertility, and a lower feed conversion ratio in affected pigs. The economic impact of *S. scabiei* var.

Table 3
Summary of *in vitro* and *in vivo* studies evaluating therapeutic failures (either lack of efficacy or established resistance) against *Psoroptes ovis* in sheep and cattle.

Host	Country	Macrocyclic lactone	Type of study	Reference
SHEEP	United Kingdom	Moxidectin	*In vitro* -Resistance confirmed	Doherty et al. (2018)
		Ivermectin Doramectin Moxidectin	*In vitro* -Resistance confirmed	Sturgess-Osborne et al. (2019)
	Argentina	Ivermectin	*In vivo* -Lack of efficacy	Larroza et al. (2020a)
			In vitro -Resistance confirmed	Soler et al. (2022)
CATTLE	Belgium	Ivermectin	*In vivo* -Lack of efficacy	Lekimme et al. (2010)
		Ivermectin Doramectin Moxidectin	*In vivo* -Lack of efficacy	Van Mol et al. (2020)
	Argentina	Ivermectin	*In vivo* -Lack of efficacy	Lifschitz et al. (2018)
		Ivermectin Doramectin	*In vivo* -Lack of efficacy	Canton et al. (2023)

suis on swine is a concern for producers, and data are available that quantify these losses. For example, a 9 % depression in the average weight gain of pigs due to sarcoptic mange was described (Cargill and Dobson, 1979). The introduction of MLs (such as IVM and DRM) for the treatment of *S. scabiei* var. suis has made infestation management easier. IVM, injected subcutaneously at a dose of 300 µg/kg body weight once or twice, has been found effective in treating infested pigs (Soll and Smith, 1987). To eradicate infestations from herds, the administration of an IVM premix in feed at a dose rate of 100 µg/kg/day over a period of 7 days, administered twice within 21 days, (7 days medication, 7 days non-medication, 7 days medication) showed optimal results (Laha, 2015). Along with treatment, strict biosecurity measures can help keep parasites out of the herd. Since the parasite can survive outside the host, cleaning facilities, with an acaricidal solution is crucial to prevent reinfection of treated pigs. One challenge in controlling *S. scabiei* var. suis is its transmission from infected sows to suckling piglets. Treating pregnant sows with IVM (at 300 µg/kg body weight, single subcutaneous injection) just before they are moved to farrowing units can control infestations in both the sows and piglets (Mercier et al., 2002). Combined administration strategies have been successful in controlling this disease; for example, a combined regimen of IVM injection and treatment in feed eradicated *S. scabiei* on a farm (Smets et al., 1999). Comparing the disposition kinetics of IVM between pigs and cattle is particularly interesting. When administered at the recommended dose via subcutaneous injection, cattle showed higher systemic availability than pigs (Lifschitz et al., 1999b). The dose dependent parameters were statistically significant after the normalization by the administered dose rate as it is shown in Fig. 4. Differences in body composition may account for variations in IVM's tissue distribution pattern, with pigs having a more extensive deposit in adipose tissue, leading to lower plasma availability (Lifschitz et al., 1999b). Hence, in some cases, repeating subcutaneous administration at day 7 post-initial treatment may be necessary for successful management of sarcoptic mange. Furthermore, differences in the duration of activity between DRM and IVM were observed for controlling *S. scabiei* var. suis infestations. DRM demonstrated double the persistent efficacy (18 days) compared to IVM (9 days) when administered at 300 µg/kg body weight in experimentally infected pigs (Arends et al., 1999). These differences in pharmacokinetic parameters, with DRM showing lower clearance and higher systemic availability than IVM, likely contribute to this variation (Lanusse et al., 1997; Lifschitz et al., 2000). While there have been reports of resistance in *S. scabiei* var. hominis to IVM, there are no reports of resistance in *S. scabiei* var. suis to MLs.

Mange, though less common than in other animals, can be a bothersome issue for horses. There are three main types of mange that affect
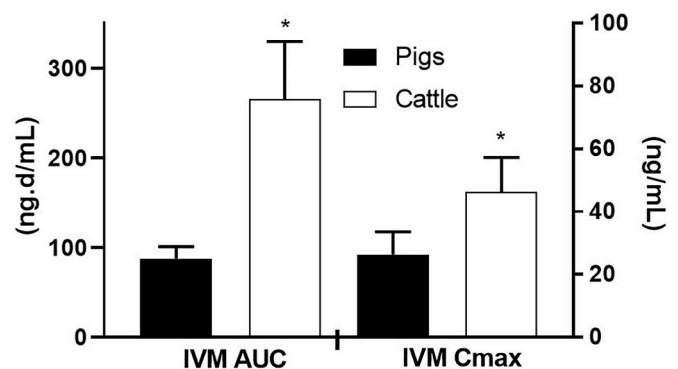

Fig. 4. Comparative ivermectin (IVM) peak plasma concentrations (Cmax) and area under the concentration vs time curve (AUC) obtained after its subcutaneous administration to pigs (0.3 mg/kg) and cattle (0.2 mg/kg). These dose-dependent parameters were normalized to the cattle dose rate. (*) Parameters are statistically different to those obtained for cattle. Adapted from Lifschitz et al. (1999b).

horses. Chorioptic Mange (Leg Mange) is the most prevalent and primarily affects the legs, causing irritation and hair loss around lower legs. Sarcoptic mange, the most severe form of mange, and psoroptic mange are less common in horses (Osman et al., 2006). Treatment typically involves the use of MLs by oral or topical treatment with bovine pour-on formulation. Oral administration of MXD paste as single dose at 0.4 mg/kg or IVM on two doses two weeks apart at 0.2 mg/kg showed clinical and parasitological cure (Osman et al., 2006). Disinfection of the surrounding environment using acaricides compounds are necessary to ensure the success of the treatment. Results from a controlled clinical trial suggest that a weekly topical use of 0.5 mg/kg of EPM for four applications was completely effective in the treatment of natural infestations of *P. equi*. No live mites were found on treated horses from days 21 (Ural et al., 2008). Treatment applied twice (Day 0 and Day 7) with a bovine pour-on formulation of MXD at 1.5 mg/kg achieved 100 % efficacy in horses affected by *C. bovis* (Brys et al., 2023). No description of resistance of mites that affect horses to MLs has been reported so far.

4. The impact of macrocyclic lactones in livestock lice management

Lice are wingless flattened insects, that live on the hair or feathers of animals. Heavy lice infestations are known as pediculosis. There are two main types of lice affecting animals, biting or chewing lice (order Mallophaga) and suckling lice (order Anoplura). Biting lice feed on skin debris and feathers, and sucking lice feed on blood (Fadok, 1984). While biting lice may infect mammals and birds, suckling lice only infect mammals. Low lice infestations normally do not represent a serious health problem. However, if lice populations increase reaching high densities, several health problems can be observed in infested animals, including itching, skin lesions and anemia. Pruritus characterizes lice infestations. In severe infestations, dermal irritation, loss of hair and local scarification can be observed, or anemia if suckling lice are involved. Lice transmission normally occurs by direct contact between animal or between herds. Lice complete their entire life cycle on animals, and they do not survive for long time off their hosts. About 3–4 weeks are required to complete the life cycle, but this can vary with species. Louse eggs are glued to hair or feathers of infested animals. Eggs hatch after approximately a period of 7–10 days. The nymphal lice stage is similar in appearance than the adult, but much smaller (Cortinas and Jones, 2006; Pérez de León et al., 2020).

MLs are used across all livestock species, but they are predominantly employed in ruminants, particularly cattle. Most research on their activity against lice has focused on this species. The main lice species infecting cattle includes the biting louse *Bovicola bovis* and three different species of suckling lice, *Linognathus vituli, Haematopinus eurysternus* and *Solenopotes capillatus*. In tropical countries, the seasons do not influence lice population and/or severity of infestation. However, in countries characterized by colder climates, the most severe infestations are usually observed in late winter and/or early spring. In cattle, suckling lice (i.e. *L. vituli, H. eurysternus*) are highly susceptible to MLs (Leaning, 1984; Schröder et al., 1985; Logan et al., 1993). Most ectoparasiticides are not active against louse eggs and the MLs are not an exception. However, the high lipid solubility and low body clearance of MLs determines their long persistence in the systemic circulation (Lanusse et al., 1997), and the effect against newly emerged nymphs. Contrarily, biting lice (i.e. *B. bovis*), are not fully eliminated from cattle after the parenteral (subcutaneous) MLs administration (Schröder et al., 1985; Logan et al., 1993). These compounds are not recommended for treating biting lice, although some commercial products in various countries claim to be an "aid in control." The eating habits of lice have been proposed as the cause of the differences in the susceptibility observed between sucking and biting lice. The high and sustained blood concentrations of MLs following subcutaneous administration to cattle (Lanusse et al., 1997) ensure that sucking lice ingest the drug. Biting lice feeds by "scraping" the outer layer of the skin and would be exposed to

lower concentrations of drug present in skin debris. After the subcutaneous treatment of cattle, IVM is extensively distributed from the bloodstream to different target tissues including the different layers of the skin (Lifschitz et al., 2000). In fact, the relationship between skin and plasma availability (measured as AUC) was between 1.22 and 2.10 (Lifschitz et al., 2000, 2018). These results indicate that biting lice would be exposed to MLs in skin debris at similar concentrations to that observed in blood. However, skin samples used to quantify IVM (Lifschitz et al., 2000, 2018) were obtained by scraping until deep layers of the skin (epidermis and dermis). It is likely that in the outer skin layer, only low ML concentration levels are accumulated, accounting for a limited exposure to drug in biting compared to suckling lice. The relative high efficacy of topical (pour-on) formulations against biting lice (Chick et al., 1993; Titchener et al., 1994; Clymer et al., 1998; Rooney et al., 1999; Skogerboe et al., 2000; Lloyd et al., 2001; Rehbein et al., 2005b) support this hypothesis. Higher skin concentrations of MLs are achieved with topical treatments (Sallovitz et al., 2003) compared to subcutaneous treatments (Lifschitz et al., 2000). This difference helps explain why topical treatments are more effective against biting lice than subcutaneous treatments in cattle. After topical administration, the lice would die from a combination of both, oral ingestion and direct contact with the drug. Furthermore, while parenteral DRM fails to prevent *L. vitulli* reinfection at 35 days post-treatment (Titchener and Purnell, 1996), topical administration achieves 100 % efficacy against *B. bovis* at 126 days post-treatment (Lloyd et al., 2001). Resistance of cattle lice to MLs has not yet been reported.

Bovicola ovis (Mallophaga) is the most common species of lice found in sheep worldwide. Sucking lice *(Anoplura)* like *L. ovillus and L. pedalis* are less common (Plant and Lewis, 2011). Goats can be infected by *B. caprae, B. limbata (Mallophaga), and L. stenopsis (Anoplura)* (Cornall and Wall, 2015; Benelli et al., 2018). The pathogenesis of these lice species is similar to that described for cattle, with the additional problem that in sheep, the irritation caused by lice leads to scratching and wool loss. In severe cases, this can affect large areas of the sheep's body, impacting both the quality and quantity of wool production. MLs are not registered for the control of lice in sheep and goats in many countries. These compounds should be effective, especially against biting lice; however, the lack of clinical studies prevents the label indication of available products (i.e., IVM parenteral solution, IVM drench solution) against lice. In Australia ABM pour-on was registered to be used against *B. ovis* (Heath and Levot, 2015).

Pigs are commonly infested by the sucking louse *H. suis* (hog louse, Anoplura), the largest blood-sucking louse found in domestic mammals. Piglets are particularly affected by *H. suis*, and severe infestations can lead to anemia and even death. Like other blood-feeding lice, *H. suis* is highly susceptible to MLs, which are approved for use in pigs via subcutaneous (IVM, MXD), intramuscular (DRM) administration at 0.3 mg/kg, and oral feed-formulation (IVM) at 0.1 mg/kg over 7 days to control both endo and ectoparasites (Barth and Brokken, 1980; Logan et al., 1996). Subcutaneous and intramuscular administrations are recommended in the neck area of pigs. It is generally advised to treat sows 7–14 days before farrowing to minimize piglet exposure to sucking lice, a practice that has proven to be an effective control measure in swine production systems.

The main lice species infesting horses include the biting louse *Bovicola equi* and the sucking louse *Haematopinus asini*. *B. equi* infestation can cause alopecia, dermal irritation, itching, and self-excoriation. Heavy *H. asini* infestations can lead to anemia and/or weight loss (Wright, 1999). The available ML formulations for horses are not approved for lice treatment in this species.

5. Concluding remarks

MLs have become a double-edged sword in the battle against ectoparasites affecting livestock animals. Their story is one of remarkable success and a cautionary tale. On the one hand, MLs have revolutionized

animal health management. Their potent broad-spectrum effectiveness against multiple ecto-endoparasites, from gastrointestinal nematodes to lice, ticks and mites has demonstrably improved animal welfare and productivity. An enormous progress on the comprehension of the relationship among disposition kinetics, tissue distribution and the patterns of antiparasitic persistence for the ML molecules in livestock animals has been achieved. The advantageous pharmacokinetic-based extended duration of action translates into fewer stressful treatments for animals and simplifies husbandry management for producers. Additionally, the safety profile of MLs at recommended doses makes them a favorable choice for routine parasite control programs. However, the widespread use of MLs has raised a significant challenge: the emergence of drug resistance by different target parasites. The large availability of generic formulations (some of them highly concentrated long-acting preparations) worldwide has unfortunately led to often indiscriminate use of these powerful therapeutic tools. Their intensive use has stimulated the genetic selection of endo and ectoparasite populations with reduced susceptibility, threatening the extraordinary effectiveness that made MLs so valuable over many years. Rational use of MLs, with targeted applications based on parasite epidemiology and pharmacological knowledge can help to maintain the antiparasitic efficacy of these compounds. Furthermore, stimulating a culture of responsible/rationale use among veterinarians and producers is crucial. The future of MLs lifespan depends on our ability to learn from wrong practices in the past. By assuming the current limitations of the MLs and adopting more integrated control approaches, it is still possible to prolong their future effectiveness. The story of the MLs is a reminder that even the most powerful tools require responsible use and continuous innovation to ensure their long-term efficacy.

CRediT authorship contribution statement

A. Lifschitz: Writing – review & editing, Writing – original draft, Conceptualization. **S. Nava:** Writing – review & editing, Writing – original draft. **V. Miró:** Writing – review & editing, Writing – original draft, Data curation. **C. Canton:** Writing – review & editing, Writing – original draft. **L. Alvarez:** Writing – review & editing, Writing – original draft. **C. Lanusse:** Writing – review & editing, Writing – original draft.

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