Anthelmintic resistance in sheep farms: Update of the situation in the American continent

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The present paper reviews the frequency of anthelmintic resistance in sheep farms in different countries of the American continent and describes some aspects that might influence the trend in sheep farms. The situation of anthelmintic resistance in sheep farms has been explored mainly in south of the continent (Argentina, Brazil and Uruguay) where sheep farming is an important industry. In those three countries, as well as in Paraguay, the first comprehensive surveys of anthelmintic resistance were performed among countries in the continent, which showed evidence of high frequency of sheep farms with anthelmintic resistance. Today, it is common to find sheep flocks with multiple-resistant worms. In North and Central America, a similar situation has been reported in sheep farms in the south of the United States of America, parts of Mexico and Costa Rica. On the other hand, other areas of the continent show low frequency of farms with anthelmintic resistance. From many areas no results have been published regarding situation on anthelmintic resistance or, alternatively, published results have received limited dissemination. Although the diagnosis of anthelmintic resistance is important for decision making of helmint management/control at the farm level, this is still an aspiration rather than a reality. For decades, researchers working on anthelmintic resistance in the American continent have expressed the need to change farmers' attitudes towards anthelmintic drugs. A common advice has been to check the anthelmintic drug efficacy regularly and reduce the dependence on these with alternative control measures. In spite of such advice, the challenge to stop/delay the advancement of anthelmintic resistance against the available anthelmintic drugs is still present. The evidence suggests that anthelmintic resistance is a growing phenomenon in the American continent. The situation described might be the tip of the iceberg, as anthelmintic resistance is still largely under-diagnosed. Hence, a different approach to tackle the advancement of anthelmintic resistance in sheep farms must be found. Awareness of farmers on the importance of diagnosis of anthelmintic resistance is not enough. Technical support schemes that provide the diagnostic service cheaply and timely must be implemented together with the research aiming at the adoption of control methods to reduce the dependence on conventional anthelmintic drugs. Unless these elements are readily available for producers, the negative consequences of anthelmintic resistance on sheep farming in America will continue to worsen with time.

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1. Introduction

A common topic for researchers working on the control of gastrointestinal nematodes of sheep is anthelmintic
resistance (AR). The presence of drug-resistant helminthes represents an important constraint for the sustainability of the current strategies of helminth control, as sheep farmers rely heavily on the constant and repetitive use of commercial anthelmintic (AH) drugs (Kaplan, 2004; Molento, 2009). These arguments seem clear for someone interested in the sustainable control of gastrointestinal nematodes in sheep farms. However, it might not be easy to understand for most people involved in sheep production in every country, about the vast continent called America. To clarify the relevance of the problem of AR in sheep farms in the American continent, it is important to identify the extent of the problem in sheep farms in the different countries. This was achieved in South America with the first major national surveys of AR performed in sheep farms (Eddi et al., 1996; Echevarria et al., 1996; Maciel et al., 1996; Nari et al., 1996; Waller et al., 1996).

In the present paper, all the references on AR surveys (national, regional or local), as well as individual farm reports retrieved from the literature from 1996 until today were analyzed. The new evidence obtained from the countries where AR was already considered a problem, is used to identify whether the previous knowledge of AR in a given country was useful to slow down the advancement of AR to other sheep farms. For other countries, the first reports of AR in sheep farms are included. The present paper also identifies countries that have not generated information on AR in sheep farms. This review is written at a crucial moment in the history of gastrointestinal nematodes control based on conventional AH drugs, as (i) two new AH molecules, with novel modes of action, are now available for sheep and may eventually be licenced for sheep market in the American continent and (ii) several groups of researchers in America work in the discovery, adaption and the eventual adoption of alternative measures to control gastrointestinal nematodes with the ultimate goal of reducing the dependence on commercial AH drugs. The objective of the present paper is to review the frequency of sheep farms with AR in the different countries of the American continent and to describe some aspects that might influence the trend of AR in sheep farms in the near future.

2. Situation regarding anthelmintic resistance in sheep farms in South American countries

The problem of AR has been explored mainly in southern countries of the continent (Argentina, Brazil and Uruguay), where sheep farming is an important industry. These southern countries, along with Paraguay, form the area of the continent where AR seems to be more prevalent and it is common to find sheep flocks with multiple resistant worms (Table 1).

It is fair to highlight the importance of the surveys of AR performed in Argentina, Brazil, Paraguay and Uruguay in the 1990s (Eddi et al., 1996; Echevarria et al., 1996; Maciel et al., 1996; Nari et al., 1996; Waller et al., 1996). The results reported in those papers have been evoked by several authors reviewing the topic of AR in the world as important evidence of high prevalence of AR in sheep farms (Nari, 2003; Kaplan, 2004; Coles et al., 2006; Jabbar et al., 2006). The reports have also been considered a good model to follow by several groups aiming at surveying AR in sheep farms worldwide. From the results of their work, the research groups in the South American surveys suggested the adoption of some concepts of nematode control, which might have been considered advanced for their time, namely to confirm the efficacy of AH drugs frequently and to reduce dependence on commercial AH drugs. After those surveys, the search for AR in sheep farms has continued in Brazil, Uruguay and Argentina and will be discussed below.

2.1. Brazil

The country, from which most surveys of AR in the American continent have been published, is Brazil (Table 1). Recent reports describe the AR situation in different regions of the country or particular groups of farms. Although the new reports performed in Brazil were not intended to describe the national situation, they confirm that the situation of AR in sheep farms is similar or even more alarming now than it was when Echevarria et al. (1996) reported their results. High levels of AR to the main AH classes are reported for many worm species. However, it is important to point out that some of the results of severe multiple AR reported in Brazil, were obtained in farms where total AH failure was already evident (da-Cruz et al., 2010). In spite of the latter, there is evidence indicating that the severity of multiple AR has reached extreme levels in some farms of Brazil. An example of this was found in a sheep farm in southern Brazil. The populations of Haemonchus spp., Trichostrongylus spp. and Ostertagia spp. showed to be resistant to the following AH drugs: levamisole 22%, moxidectin 1%, albendazole 10%, ivermectin 1%, nitroxynil 34%, disophenol 20%, trichlorphon 10% and closantel 10%. These helminth populations were also resistant to a triple combination product with ivermectin, levamisole and albendazole (Cezar et al., 2010). The same type of data has also been recently obtained in a controlled efficacy trial performed in Brazil by Almeida et al. (2010). These authors used a strain of Haemonchus contortus isolated from a farm treating with moxidectin and with a history of AR against ivermectin, levamisole and oxendazole. They also infected the animals with a Trichostrongylus colubriformis strain isolated from a farm treating with trichlorfon (no mention of its AR history was provided). Their results showed that the H. contortus strain was resistant to albendazole, levamisole, ivermectin, closantel, moxidectin and thriclorfon. The same was found for the T. colubriformis strain tested. That was the first report in Brazil of macrocyclic lactone resistance in T. colubriformis obtained with a controlled efficacy test.

2.2. Argentina

After the work reported by Eddi et al. (1996), a second national survey of AR was funded by the FAO (Caracostantogolo et al., 2005). This time, the national survey, which also included cattle farms, considered fewer sheep farms than previously. The survey of 2005 showed a slight increase in the frequency of sheep farms showing evidence of AR for the broad spectrum AH drugs; benzimidazoles, ivermectin and closantel. An interesting approach
of that survey was the inclusion of other research activities aiming at the development of in vitro assays and molecular techniques for future diagnostic studies of AR. It also considered the study of different selective AH treatment schemes and other non-conventional tools for the control of gastrointestinal nematodes.

2.3. Uruguay

There are recent reports of AR in Uruguay, showing a tendency towards the expansion of AR in more sheep farms of that country (Bonino and Mederos, 2003). One of the surveys described by those authors was obtained from a large quantity of farmers (n = 82) and suggested that the vast majority of sheep farms (>80%) were resistant to the four main AH groups used in sheep. The problem of AR in sheep farms of Uruguay has been reported to the public as a major problem for the industry (Mederos, 2002). At present, governmental organizations in charge of animal health are performing a national effort to implement integrated parasite control strategies to mitigate the effects of AR.

2.4. Other countries

The sole report found for Paraguay is that of Maciel et al. (1996) mentioned above (Table 1). A couple of reports on AR have been documented in Venezuela (Morales and Pino, 2001; Muñoz et al., 2008) and a third one in Peru (Tang-Ploog, 2005). However, the reports from Venezuela and Peru cannot be considered as conclusive evidence in those countries. The situation of AR in sheep farms in all the other countries of South America is still unknown due to the lack of published reports.

3. Situation regarding anthelmintic resistance in sheep farms in North American, in Central American and in Caribbean countries

3.1. Canada

This country was reported as an area where macrocyclic lactones were still effective in sheep farms (Kaplan, 2004). However, that same author places Canada as a country with presence of AR against benzimidazoles and levamisole in sheep farms. According to Guthrie et al. (2010), the reports on AR in Canada are scarce and the lack of reports is the result of several factors: (i) extreme temperatures commonly recorded in Canada, (ii) diversity in management practices, (iii) less frequent use of AH drugs compared to other countries and (iv) the relatively small size of individual farms and national sheep flock compared to other countries. However, the same authors mentioned a report of multi-drug resistance of Haemonchus spp. to ivermectin and albendazole in a sheep farm (Glauser et al., 2007) and also commented that the existence of reports of AH failure on other farms could suggest that AR might be a problem in Canada.
3.2. United States of America

The trial reported by Howell et al. (2008) provides evidence about the situation of AR in the United States of America. This work is a good example of collaboration between different teams of researchers in eight different states in the south of that country, as well as in Puerto Rico and St Croix. The authors described a survey performed with a commercial in vitro technique (larval development assay). That is also a salient feature of the trial, as this is the only report of AR that used an in vitro technique in the American continent. All the other workers elsewhere used the conventional Faecal Egg Count Reduction Tests following the guidelines by Coles et al. (1992). The findings of Howell et al. (2008) showed strong evidence of AR as a serious problem in sheep farms throughout the southeastern United States (Table 1). These authors also mentioned that, owing to the frequent movement of animals among regions, prevalence of resistance in other regions of the United States would also likely be high.

3.3. Mexico

As it is the case for other trials mentioned above, the surveys performed in Mexico were not designed to provide evidence of the AR situation in sheep farms at national level. Several independent surveys have been performed, mainly in the states of the Gulf of Mexico, with a few performed in the highlands of central Mexico. The different surveys show that the situation of AR depends on the region of the country. Those studies performed under hot humid conditions tended to show higher frequencies of sheep farms with AR (Torres-Acosta et al., 2003a, 2007; Nuncio-Ochoa et al., 2005). Meanwhile, the surveys performed in the highland areas with temperate dry conditions showed low frequencies of farms with AR (Garcia-Flores et al., 2003; Montalvo-Aguilar et al., 2006). Another survey with low frequency of resistance was obtained with low income farmers (Torres-Acosta et al., 2003b). In general, the situation of AR seems not to be particularly alarming, with the exception of the survey performed in Tabasco where AR was found to be severe (Nuncio-Ochoa et al., 2005). Isolated reports of farms with AR have been obtained in different states of Mexico, but, again, these were farms where resistance was already suspected from repeated treatment failures (Gonzalez-Garduno et al., 2003; Cuellar-Ordaz, 2009). Animal health authorities in Mexico are currently designing a national survey of AR in sheep farms to consider a valid sample size and the randomization of the farms to be surveyed.

3.4. Other Central American and Caribbean countries

The first reports of AR in sheep farms in Cuba and Nicaragua were published by Arece et al. (2004) and Rimbaud et al. (2005), respectively (Table 1). These authors did not aim at investigating the situation of AR in their countries. Arece et al. (2004) discussed that some AH drugs were not readily available in Cuba and this could have explained why this drugs might not have created resistant parasitic strains yet. A contrasting situation was found in Costa Rica (Maroto et al., 2009), where a high frequency of AR against benzimidazoles and ivermectin was reported in the farms surveyed (Table 1).

4. What has caused the current level of knowledge regarding anthelmintic resistance among different countries of America?

Within the American continent, the relative importance of the sheep production industry in each country is different. The present review shows that most of the research on AR in sheep farms has been performed in those countries of America where sheep population is over 2,000,000 animals (FAO-STAT, 2011). However, even some countries with a sheep population over that, have not reported any information or survey data on AR in sheep farms (Bolivia, Chile, Colombia, Peru). It is important to identify if lack of information is due to (i) absence of research groups working in the field of AR, (ii) lack of technical capabilities or (iii) public unavailability of otherwise available results. A recent review discussed the possible causes for lack of AR diagnosis in the countries of Latin America (Torres-Acosta et al., 2012). If the evidence on the frequency of sheep farms with AR nematodes is missing for most countries in America one can ask why the research on sheep parasitology performed in America in the last two decades has been mainly focused on the development of different methods to reduce the dependence on commercial AH drugs? It is important to accept that AR is a reality for farmers in some regions of America as described above. However, the impact of AR on the productivity of sheep farms is still not evaluated and is difficult to perceive for most farmers. Although the possibility of abandonment of sheep farming systems due to resistant helminthes has been discussed (Maciel et al., 1996), no record has been published so far to identify the magnitude of the problem in a given area. Undoubtedly, it will be too late to start implementing strategies to control the problem when multiple AR is already present.

5. Joining efforts for the diagnosis of anthelmintic resistance

The lack of diagnosis of AR in many countries of the American continent might be attributed, at least in part, to the lack of technical knowledge and/or the lack of financial resources to perform the surveys. For all the research groups, financial support to perform this type of research is more limited each year. Thus, it is clear that researchers should warn and try to convince their authorities about the seriousness of the AR problem and the importance of proposing alternative measures to prevent the rapidly spreading problem of AR in their countries. However, instead of isolated efforts in each region and country, it is better to collaborate with other research groups in other countries pursuing the same goals. A good example of a joint effort for a common goal is the creation of the ‘Consortium of Anthelmintic Resistance and Susceptibility’ (CARS). Four American institutions (two from Brazil, one from Canada and one from United States of America) are active partners of the consortium together with institutions from Europe, Australia and New Zealand. Objective of the CARS
group is to have better markers for anthelmintic resistance that can be used to monitor the spread of resistance in parasite populations in animals and humans (Prichard et al., 2007). The consortium is also trying to develop genotyping assays to determine the frequencies of genetic changes (single-nucleotide polymorphisms), causing or associated with AR in populations of parasitic nematodes and other helminths. Putting together the efforts of more people within clear collaboration schemes can help to obtain more funding for research purposes and, eventually, will bring better results than groups working alone.

6. Standing at the cross-roads: the arrival of new anthelmintic molecules to America

Until recently, it was common to find review articles on AR reporting that no new AH product was going to appear in the sheep market in the foreseeable future (Kaplan, 2004; Wolstenholme et al., 2004; Coles et al., 2006; Waller, 2006). In fact, there has not been a new anthelmintic class for ruminants appearing on the marketplace for a long period (Waller, 2006). It was until very recently that the sheep industry in the world welcomed the arrival of two new AH drugs, both with novel modes of action (Kaminsky et al., 2008; Little et al., 2010). Monepantel (amino-acetonilide derivative class) was launched in 2009, whilst derquantel (spiroindole class) was launched in 2010. Both products were first approved for commercial use in New Zealand, possibly due to the importance of that market in the sheep world. One of the new compounds, monepantel, has already been tested in Argentina, Brazil and Uruguay with good results (Bustamante et al., 2009). The second product might eventually arrive to the American continent in the future. Both pharmaceutical companies are introducing their product together with clear campaigns about the need to preserve the efficacy of the new molecules. Scientific papers, brochures and Internet websites are describing the importance of the problem and how to reduce the development of resistance at farm level (Leathwick and Hosking, 2009; Leathwick et al., 2009). Maybe sheep farmers, the pharmaceutical industry and the other stakeholders within the sheep industry are now standing at a cross-road where they must decide to continue in the same well-known path leading to the creation of resistant worms for these new molecules in a short period of time or to follow a new path leading to the sustainable use of their novel compounds.

7. Implementation of alternative measures to control gastrointestinal nematodes in countries of America

Sustainable use of commercial AH drugs will depend on the application of different methodologies that may help to reduce the dependence on the AH drugs (Jackson and Miller, 2006; Torres-Acosta and Hoste, 2008; Molento, 2009). In the American continent, those same research groups investigating AR in different countries have also invested time and effort working on alternative approaches for the control of gastrointestinal nematodes in sheep. As a result, the majority of the scientific papers published in the last decade by the research groups working on gastrointestinal nematodes parasites of sheep in American countries are related to the topic of alternative methods for the control of gastrointestinal nematodes (Torres-Acosta et al., 2012). In spite of the clear efforts invested, the majority of these methods are still not adapted for the common farmer. Indeed, the adaptation of the alternative methods will need more funding to perform more on-farm trials in different countries. However, it is not only a matter of funding, but a problem of regulations as well. The guidelines to declare the efficacy of any commercial AH drug against a given parasite of a given parasitic stage are clear (Wood et al., 1995). However, the procedures for commercial AH drugs cannot be directly used to validate the efficacy of most alternative tools against gastrointestinal nematodes (Ketzis et al., 2006). The creation of ad hoc procedures to evaluate the efficacy against gastrointestinal nematodes for the different alternative methods is required. To achieve this goal, a considerable effort from farmers, parasitologists and government authorities will be required in order to build the new thresholds to declare efficacy for the different methods of control. That becomes more complicated considering that the alternative methods of gastrointestinal nematodes control are proposed as concurrent tools rather than single possibilities (Krecek and Waller, 2006).

Not all the alternative methods of gastrointestinal nematodes control need to provide evidence of efficacy to government regulatory bodies before their implementation is possible. Supplementary feeding (Knox et al., 2006), grass management (rotation and/or alternation of animal species) (Rocha et al., 2008; Mahieu and Aumont, 2009), bioactive fodder (used as nutraceuticals) (Alonso-Díaz et al., 2010) and the genetic selection of resilient or resistant animals (Amarante et al., 2009) are some methods that can also help to reduce the dependence on AH drugs. However, it is not possible to declare what level of improvement is expected for each of these strategies, as it will depend on a number of factors, e.g. breed of animals, nutritional status of the hosts, season and climatic conditions of the area, farm size or production level expected from the respective group of animals. Beyond their efficacy against gastrointestinal nematodes, the implementation of all the techniques mentioned here will depend mainly on the economic viability of the strategy (alone or in combination) (Martínez-Ortiz-de-Montellano et al., 2007).

A final consideration must be given to the selective use of AH treatments in sheep flocks. The uptake of the FAMACHA© technique in the United States of America (Kaplan et al., 2004; Burke et al., 2007) and Brazil (Molento et al., 2009; Abrão et al., 2010) can be considered as good examples of successful technology transfer efforts. Other countries in America are studying the possibility of using FAMACHA© to help in the farmer’s decision to treat their animals with AH drugs (Mahieu et al., 2007). The small flock size in sheep farms in many areas of different countries of America and the presence of abundant H. contortus populations seem suitable to perform the selective treatment using the FAMACHA© chart. Besides, it is still possible to improve the use of the FAMACHA© by combining it with body condition score and faecal egg counts to reduce the number of AH treatments in those anaemic animals that have low gastrointestinal nematodes
infections (Torres-Acosta et al., 2009). Similar attempts to avoid the treatment of anaemic animals with low infections have been investigated recently in Venezuela (Morales et al., 2008). The selective treatment schemes can help to reduce the use of conventional AH drugs and this helps to increasing the size of the refugia in the farm. The expected result is to delay development of resistant worms against the commercial AH drugs currently available (Wolstenholme et al., 2004; Leathwick and Hosking, 2009; Leathwick et al., 2009) and also the new AH molecules. However, untreated animals might show a negative impact on their productivity due to sub-clinical infections. Therefore, selective use of AH treatments needs to be evaluated on a farm-to-farm basis and always in the light of its economic feasibility and practicality in the field.

8. Concluding remarks
The current situation of AR in sheep farms in the American continent is contrasting. Some countries or areas within countries have a high frequency of sheep farms with AR and this situation has been deteriorating with time. Advancement of the AR problem occurred, in spite of the previous knowledge on the AR situation in those countries. Meanwhile, a few areas of the continent showed low frequency of sheep farms with AR. Also, several countries have not published evidence on their situation of AR in sheep farms. The information suggests that the efforts of AR diagnosis and the level of awareness about the problem of AR amongst sheep farmers and other stakeholders in the sheep industry are still insufficient to delay the development of AR in more farms. It is evident that farmers need to reduce their dependence on conventional AH drugs as the sole method of control against gastrointestinal nematodes. For that purpose, the selective use of AH treatments combined with one or more alternative approaches of gastrointestinal nematodes control must be adapted to the conditions of the farmers. Sheep farmers and researchers will need to collaborate in such implementation process. Otherwise, sustainability of available and the forthcoming AH molecules will not be feasible.

Conflict of interest statement
The authors of this manuscript have no financial or personal relationships with other people or organizations that could inappropriately influence or bias the content of the paper.

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