Short Communication

Widespread anthelmintic resistance in European farmed ruminants: a systematic review

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Anthelmintic resistance (AR) in gastrointestinal nematodes (GINs) has been reported worldwide in multiple nematode and livestock species (Kaplan and Vidyashankar 2012) and is a major constraint on production on affected farms (Sutherland and others 2010, Miller and others 2012). In the UK and Ireland, for example, AR in GINs and anthelmintic treatment failure is widespread in sheep (e.g. Bartley and others 2003, Keane and others 2014) and increasingly reported in cattle (e.g. O'Shaughnessy and others 2014). There is, therefore, a need to develop and adopt GIN control strategies that maintain the efficacy of anthelmintics and to identify risk factors for the development of AR.

Environmental constraints on farm management and the survival of nematodes in refugia appear to play an important role in the development of AR. In a random survey of sheep farms in Norway, AR was found only in coastal regions (Domke and others 2012a). Papadopoulos and others (2001) observed a higher incidence of AR on isolated Greek islands, suggesting that drought hastens the development of AR. In contrast, Rinaldi and others (2014) observed high anthelmintic efficacy in sheep in southern Italy despite the Mediterranean climate. This was attributed to the low number of anthelmintic treatments (usually two per year) and the absence of anthelmintic treatments during periods of drought, when environmental constraints on the free-living stages are highest. Calvete and others (2012) identified an association between AR, distance between farms with AR, management and bioclimatic variables on sheep farms in Aragon, Spain. In particular, the association between AR and climatic conditions was attributed to the application of anthelmintic treatments during the winter months, which increases the selection pressure on the already depleted population of nematodes in refugia. Such spatial analyses provide useful insights into risk factors for AR, but their application is likely to be limited outside of the region studied. Pan-European spatial analysis and modelling of the distribution of AR may enable the elucidation of common risk factors for the development of AR in European livestock.

A systematic review of peer-reviewed literature was undertaken to record the current distribution of AR in the major GINs (*Teladorsagia* species, *Trichostrongylus* species, *Haemonchus contortus*, *Ostertagia ostertagi* and *Cooperia oncophora*) infecting goats, sheep and cattle in Europe (defined as the EU, European Economic Area and Switzerland). The ISI Web of Science database was explored using the keywords "anthelmintic resistance" (last searched 2 Oct 14). No restrictions were placed on publication dates. The search yielded 1852 publications, of which 120 publications were selected based on title and abstract, excluding studies on non-ovine, non-bovine or non-caprine hosts and nematodes, non-European studies and studies where AR arose through artificial selection. A further nine reports of AR were identified from citations, MSc/PhD theses and authors' unpublished data. Of these publications, 73 provided reports of AR in cattle, sheep or goats assessed in accordance with the World Association for the Advancement of Veterinary Parasitology guidelines (Coles and others 1992) and stated the country or region where the farms were located.

AR in GINs, assessed primarily using faecal egg count reduction tests, is widespread in Europe (see online supplementary figure). Overall, AR was reported in all five GIN genera and in 16 countries throughout Europe (see online supplementary figure and table). Multiple drug resistance (MDR) in the three main GIN genera infecting sheep and goats was reported in 10 countries (see online supplementary table). Not all studies tested multiple anthelmintics, and therefore, MDR is likely to be more widespread. Monepantel resistance was reported on sheep farms in the Netherlands in November 2014 (Anon 2014) but was not included in the systematic review as details regarding the methods used to assess resistance were not available at the time of writing. AR against derquantel had not been reported in Europe at the time of writing. However, due to publication and sample selection bias, the absence of reports of AR in some regions may simply be due to a lack of monitoring and AR cannot be considered absent elsewhere. Heterogeneity in the distribution of AR in Europe might also depend on the lack of standardised procedures for surveys and detection of AR on farms and in laboratories.

The estimated prevalence of AR varied by region, anthelmintic class and host. Random surveys of sheep farms have detected albendazole resistance on 11 per cent of farms in Norway (n=19; Domke and others 2012a); ivermectin, benzimidazole and levamisole resistance on 23 per cent, 3.7 per cent and 7.4 per cent of farms, respectively, in Slovakia (n=27; Čerňanská and others 2006); and benzimidazole and levamisole resistance

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on 83 per cent and 50 per cent, respectively, of farms in western France (n=23; Chartier and others 1998). In the latter study, benzimidazole resistance was also detected on 93 per cent of goat farms (n=15). A further random survey of dairy goat farms in southwestern France detected benzimidazole resistance on 83 per cent of farms and multiple resistance to benzimidazole and levamisole on 11 per cent of farms (n=18; Chartier and others 2001). A sample size-weighted mean prevalence of benzimidazole resistance in GINs in sheep and goats of 50.1 per cent was estimated from the above four studies. Excluding goats, the sample size-weighted mean prevalence of benzimidazole resistance in sheep GINs was 32.1 per cent. Insufficient data were available to estimate mean prevalence for other anthelmintic classes and cattle. The prevalence of AR has also been estimated elsewhere, for example, treatment failure has been identified on 51 per cent of Irish sheep farms surveyed (Keane and others 2014) and 64 per cent of Scottish sheep farms surveyed (Bartley and others 2003). These studies provide valuable prevalence estimates, but the differences in sample (farm) selection methods introduce potential sample selection bias and may affect estimates and comparability between regions. For example, Domke and others (2012a) observed AR on 33 per cent of randomly selected sheep flocks and 80 per cent of non-randomly selected sheep flocks in the Rogaland region of Norway. Therefore, it is recommended that future prevalence surveys follow a random or stratified sampling approach where possible to reduce sample selection bias.

The biases described above currently prevent robust spatial meta-analysis of AR in Europe and restrict the spatial analysis that can be undertaken. In addition, since spatial analysis is rarely the purpose of a study into AR and due to data protection responsibilities, cases are usually reported at a country or regional level. Due to the significant within-region heterogeneity in the distribution of AR (e.g. Calvete and others 2012), data with a higher spatial resolution are required.

Taken together, the peer-reviewed literature paints a picture of widespread AR in Europe with the potential for high regional prevalence. Veterinarians should continue to promote sustainable anthelmintic use (e.g. Abbott and others 2012, Charlier and others 2014), even on farms where AR is not suspected. Continued surveillance of AR in Europe, reporting the absence of resistance (Paraud and others 2010, Rinaldi and others 2014) and reporting cases in a way that enables spatial meta-analysis, will aid in the future identification of risk factors and evaluation of sustainable nematode control practices.

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