Widespread anthelmintic resistance in European farmed ruminants: a systematic review

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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 2 per year) and 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* spp., *Trichostrongylus* spp., *Haemonchus contortus*, *Ostertagia ostertagi* and *Cooperia oncophora*) infecting goats, sheep and cattle in Europe (defined as the

European Union (EU), European Economic Area (EEA) and Switzerland). The ISI Web of Science database was explored using the keywords “anthelmintic resistance” (last searched 02/10/14). No restrictions were placed on publication dates. The search yielded 1,852 publications, of which 120 publications were selected based on title and abstract, excluding studies on non-ovine, -bovine or -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 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 (FECRT), is widespread in Europe (supplementary figure). Overall, AR was reported in all five GIN genera and in 16 countries throughout Europe (supplementary figure and table). Multiple drug resistance (MDR) in the three main GIN genera infecting sheep and goats was reported in 10 countries (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 standardized 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% of farms in Norway (n=19; Domke and others 2012a), ivermectin, benzimidazole and levamisole resistance on 23%, 3.7% and 7.4% of farms, respectively, in Slovakia (n=27; Čerňanská and others 2006), and benzimidazole and levamisole resistance on 83% and 50%, respectively, of farms in Western France (n=23; Chartier and others 1998). In the latter study, benzimidazole resistance was also detected on 93% of goat farms (n=15). A further random survey of dairy goat farms in Southwestern France detected benzimidazole resistance on 83% of farms, and multiple resistance to benzimidazole and levamisole on 11% 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% was estimated from the above four studies. Excluding goats, the sample size-weighted mean prevalence of benzamidazole resistance in sheep GINs was 32.1%. Insufficient data were available to estimate mean prevalence for other anthelmintic classes and cattle. The prevalence of AR has also been estimated elsewhere e.g. treatment failure has been identified on 51% of Irish sheep farms surveyed (Keane and others 2014) and 64% of Scottish sheep farms surveyed (Bartley and others 2003). These studies provide valuable prevalence estimates but 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% of randomly selected sheep flocks and 80% 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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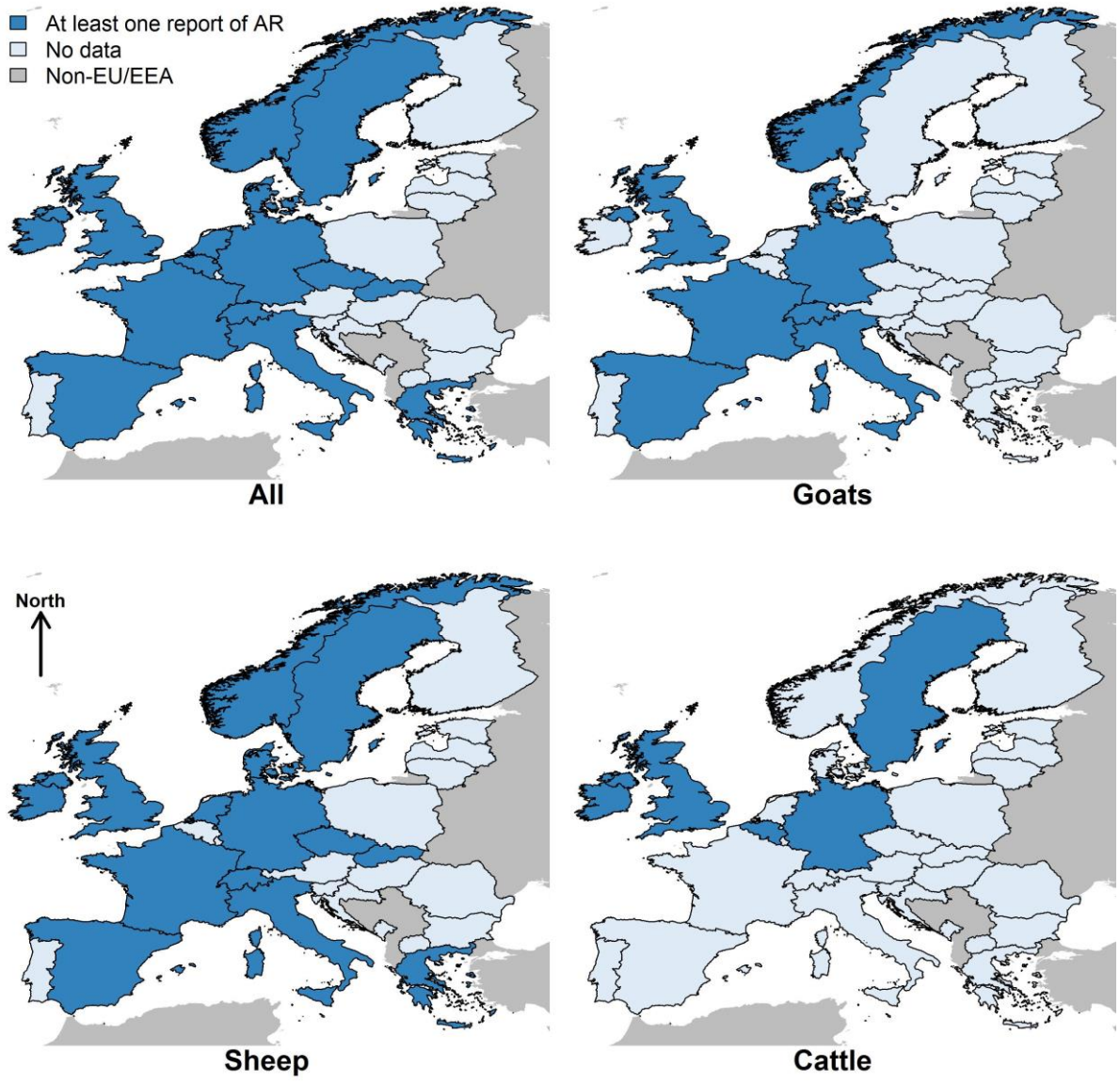
Supplementary figure. The distribution of reported cases of anthelmintic resistance (AR) in the European Union, European Economic Area and Switzerland, at national level, based on the systematic review. Shaded countries had at least one reported case of AR. Note that regional distribution within countries is not plotted: see supplementary table for details of drug classes and GIN genera/species, and individual references for specific locations and apparent prevalence. No data were available for Iceland (not shown).



345 **Supplementary table.** Summary of anthelmintic resistance reported in five major gastrointestinal
346 nematode species/genera infecting goats, sheep and cattle in Europe.

AH class[a]	Host	Region	References
***Teladorsagia* spp.**			
BZ	**Sheep**	Czech Republic, Denmark, France, Greece, Ireland, Italy, Netherlands, Norway, Slovakia, Spain, UK	Alvarez-Sánchez and others 2006, Bartley and others 2004, 2006, Bjørn and others 1991, Boersema and others 1987, Borgsteede and others 1997, 2007, Britt & Oakley 1986, Cawthorne and Whitehead 1983, Cawthorne and Cheong 1984, Čerňanská and others 2006, Chartier and others 1998, Díez-Baños and others 2008, Domke and others 2012a,b, Geurden and others 2014, Good and others 2012, Grimshaw and others 1994, Hong and others 1992, 1996, Maingi and others 1996b, Martínez-Valladares and others 2012a, McMahon and others 2013, Mitchell and others 2010, Taylor and others 2009, Traversa and others 2007, Vadlejch and others 2014
	Goats	France, Denmark, Italy, Netherlands, Norway, Spain, UK	Borgsteede and others 1996, Chartier and others 1998, 2001, Domke and others 2012a, Hong and others 1996, Jackson and others 1992, Maingi and others 1996a, Requejo-Fernández and others 1997, Zanzani and others 2014
ML	**Sheep**	Czech Republic, Denmark, Italy, Netherlands, Slovakia, Spain, Sweden[b], UK	Alvarez-Sánchez and others 2006, Bartley and others 2004, 2006, Borgsteede and others 1997, Čerňanská and others 2006, Díez-Baños and others 2008, Höglund and others 2009, Maingi and others 1996b, Martínez-Valladares and others 2012a, b, McMahon and others 2013, Taylor and others 2009, Traversa and others 2007, Vadlejch and others 2014
	Goats	Denmark, Italy, Switzerland, UK	Jackson and others 1992, Maingi and others 1996a, Murri and others 2014, Zanzani and others 2014
LEV	**Sheep**	Denmark, France, Greece, Ireland, Italy, Netherlands, Spain, UK	Alvarez-Sánchez and others 2006, Bartley and others 2004, 2006, Bjørn and others 1991, Borgsteede and others 1997, Chartier and others 1998, Geurden and others 2014, Good and others 2012, Hong and others 1996, Maingi and others 1996b, Martínez-Valladares and others 2012b, McMahon and others 2013, Mitchell and others 2010, Taylor and others 2009, Traversa and others 2007
	Goats	Denmark, France, UK	Chartier and others 2001, Hong and others 1996, Maingi and others 1996a

MDR	**Sheep**	Denmark, Greece, Ireland, Italy, Netherlands, Spain, UK	Alvarez-Sánchez and others 2006, Bartley and others 2004, 2006, Borgsteede and others 1997, Geurden and others 2014, Good and others 2012, Maingi and others 1996b, Martínez-Valladares and others 2012b, Mitchell and others 2010, Sargison and others 2005, 2007, 2010, Taylor and others 2009, Traversa and others 2007, Wilson & Sargison 2007
	Goats	Denmark, France, UK	Chartier and others 2001, Jackson and others 1992, Maingi and others 1996a

***Trichostrongylus* spp.**

BZ	**Sheep**	Denmark, France, Greece, Ireland, Italy, Netherlands, Norway, Slovakia, Spain, UK	Alvarez-Sánchez and others 2006, Bjørn and others 1991, Boersema and others 1987, Borgsteede and others 1997, 2007, Čerňanská and others 2006, Chartier and others 1998, Díez-Baños and others 2008, Domke and others 2012a, Geurden and others 2014, Good and others 2012, Maingi and others 1996b, Martínez-Valladares and others 2013, McMahon and others 2013, Mitchell and others 2010, Palcy and others 2010, Taylor and others 2009, Traversa and others 2007
	Goats	Denmark, France, Italy, Netherlands, Norway	Borgsteede and others 1996, Cabaret and others 1995, Chartier and others 1998, 2001, Cringoli and others 2007, Domke and others 2012a, Maingi and others 1996a, Paraud and others 2009, Zanzani and others 2014
ML	**Sheep**	Denmark, Greece, Italy, Netherlands, Slovakia, Spain, UK	Alvarez-Sánchez and others 2006, Bartley and others 2006, Borgsteede and others 1997, Čerňanská and others 2006, Geurden and others 2014, Maingi and others 1996b, Martínez-Valladares and others 2013, McMahon and others 2013, Traversa and others 2007
	Goats	Denmark, Italy, Switzerland	Artho and others 2007, Maingi and others 1996a, Murri and others 2014, Zanzani and others 2014
LEV	**Sheep**	Denmark, France, Greece, Ireland, Italy, Netherlands, Spain, UK	Alvarez-Sánchez and others 2006, Bjørn and others 1991, Borgsteede and others 1997, Chartier and others 1998, Geurden and others 2014, Good and others 2012, Maingi and others 1996b, Martínez-Valladares and others 2013, McMahon and others 2013, Mitchell and others 2010, Taylor and others 2009, Traversa and others 2007
	Goats	Denmark, France	Chartier and others 2001, Maingi and others 1996a, Paraud and others 2009

MDR	**Sheep**	Denmark, Germany, Greece, Ireland, Italy, Netherlands, Spain, UK	Alvarez-Sánchez and others 2006, Borgsteede and others 1997, Geurden and others 2014, Good and others 2012, Maingi and others 1996b, Martínez-Valladares and others 2013, Mitchell and others 2010, Traversa and others 2007, Voigt and others 2012
	Goats	Denmark, France	Chartier and others 2001, Maingi and others 1996a
Haemonchus contortus			
BZ	**Sheep**	France, Germany, Greece, Netherlands, Norway, Slovakia, Sweden, Switzerland, UK	Boersema and others 1987, Borgsteede and others 1997, 2007, Borgsteede and Duyn 1989, Cawthorne and Cheong 1984, Čerňanská and others 2006, Domke and others 2012a,b, Gallidis and others 2012, Geurden and others 2014, Grimshaw and others 1994, Hertzberg and others 2000, Höglund and others 2009, Hong and others 1992, Jordi 1980, Meyer 2001, Scheuerle and others 2009
	Goats	France, Netherlands, Switzerland	Borgsteede and others 1996, Cabaret and others 1995, Chartier and others 1998, 2001, Hertzberg and others 2000, Meyer 2001, Schnyder and others 2005
ML	**Sheep**	Czech Republic, Germany, Greece, Italy, Netherlands, Slovakia, Switzerland	Artho and others 2007, Borgsteede and others 1997, 2007, Čerňanská and others 2006, Geurden and others 2014, Scheuerle and others 2009, Vadlejch and others 2014, Zanzani and others 2014
	Goats	Germany, Switzerland	Artho and others 2007, Murri and others 2014, Scheuerle and others 2009, Schnyder and others 2005
LEV	**Sheep**	Greece, Netherlands	Borgsteede and others 1997, Geurden and others 2014
	Goats	France	Chartier and others 2001
MDR	**Sheep**	Greece, Netherlands	Borgsteede and others 1997, Geurden and others 2014, Van den Brom and others 2013
	Goats	France, Switzerland	Chartier and others 2001, Schnyder and others 2005
Ostertagia ostertagi			
BZ	**Cattle**	Belgium[b]	Borgsteede and others 1992

ML	**Cattle**	Germany, Sweden	Demeler and others 2009
Cooperia oncophora			
ML	**Cattle**	Belgium, Germany, Ireland, Sweden, UK	Areskog and others 2013, Bartley and others 2012, Coles and others 1998, Demeler and others 2009, El-Abdellati and others 2010a,b, McArthur and others 2011, O'Shaughnessy and others 2014, Stafford & Coles 1999
Other[c]			
BZ	**Sheep**	Ireland, Netherlands, Slovakia, Spain, UK	Bartley and others 2003, Borgsteede 1986, Burgess and others 2012, Calvete and others 2012, Grimshaw and others 1994, Keane and others 2014, Praslička and others 1994, Várady and others 2006, de Waal, T. and others unpublished observations
LEV	**Sheep**	Ireland, UK	Burgess and others 2012, Grimshaw and others 1994, Keane and others 2014
ML	**Sheep**	Ireland	Keane and others 2014
MDR	**Sheep**	UK	Burgess and others 2012

[a]AH = anthelmintic, BZ = benzimidazoles (including pro-BZs), ML = macrocyclic lactones, LEV = levamisole, MDR = multiple drug resistance
[b]Suspected resistance
[c]Other minor species, or species/genera not identified

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