

# 1 **Widespread anthelmintic resistance in European farmed ruminants: a systematic review**

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

28 Environmental constraints on farm management and the survival of nematodes *in refugia* appear to  
29 play an important role in the development of AR. In a random survey of sheep farms in Norway, AR  
30 was found only in coastal regions (Domke and others 2012a). Papadopoulos and others (2001)  
31 observed a higher incidence of AR on isolated Greek islands, suggesting that drought hastens the  
32 development of AR. In contrast, Rinaldi and others (2014) observed high anthelmintic efficacy in  
33 sheep in southern Italy, despite the Mediterranean climate. This was attributed to the low number  
34 of anthelmintic treatments (usually 2 per year) and absence of anthelmintic treatments during  
35 periods of drought, when environmental constraints on the free-living stages are highest. Calvete  
36 and others (2012) identified an association between AR, distance between farms with AR,  
37 management and bioclimatic variables on sheep farms in Aragon, Spain. In particular, the association  
38 between AR and climatic conditions was attributed to the application of anthelmintic treatments  
39 during the winter months, which increases the selection pressure on the already depleted  
40 population of nematodes *in refugia*. Such spatial analyses provide useful insights into risk factors for  
41 AR but their application is likely to be limited outside of the region studied. Pan-European spatial  
42 analysis and modelling of the distribution of AR may enable the elucidation of common risk factors  
43 for the development of AR in European livestock.

44 A systematic review of peer-reviewed literature was undertaken to record the current distribution of  
45 AR in the major GINs (*Teladorsagia* spp., *Trichostrongylus* spp., *Haemonchus contortus*, *Ostertagia*  
46 *ostertagi* and *Cooperia oncophora*) infecting goats, sheep and cattle in Europe (defined as the

47 European Union (EU), European Economic Area (EEA) and Switzerland). The ISI Web of Science  
48 database was explored using the keywords “anthelmintic resistance” (last searched 02/10/14). No  
49 restrictions were placed on publication dates. The search yielded 1,852 publications, of which 120  
50 publications were selected based on title and abstract, excluding studies on non-ovine, -bovine or -  
51 caprine hosts and nematodes, non-European studies and studies where AR arose through artificial  
52 selection. A further nine reports of AR were identified from citations, MSc/PhD theses and authors’  
53 unpublished data. Of these publications, 73 provided reports of AR in cattle, sheep or goats assessed  
54 in accordance with World Association for the Advancement of Veterinary Parasitology guidelines  
55 (Coles and others 1992) and stated the country or region where the farms were located.

56 AR in GINs, assessed primarily using faecal egg count reduction tests (FECRT), is widespread in  
57 Europe (supplementary figure). Overall, AR was reported in all five GIN genera and in 16 countries  
58 throughout Europe (supplementary figure and table). Multiple drug resistance (MDR) in the three  
59 main GIN genera infecting sheep and goats was reported in 10 countries (supplementary table). Not  
60 all studies tested multiple anthelmintics and, therefore, MDR is likely to be more widespread.  
61 Monepantel resistance was reported on sheep farms in the Netherlands in November 2014 (Anon  
62 2014) but was not included in the systematic review as details regarding the methods used to assess  
63 resistance were not available at the time of writing. AR against derquantel had not been reported in  
64 Europe at the time of writing. However, due to publication and sample selection bias, the absence of  
65 reports of AR in some regions may simply be due to a lack of monitoring and AR cannot be  
66 considered absent elsewhere. Heterogeneity in the distribution of AR in Europe might also depend  
67 on the lack of standardized procedures for surveys and detection of AR on farms and in laboratories.

68 The estimated prevalence of AR varied by region, anthelmintic class and host. Random surveys of  
69 sheep farms have detected albendazole resistance on 11% of farms in Norway (n=19; Domke and  
70 others 2012a), ivermectin, benzimidazole and levamisole resistance on 23%, 3.7% and 7.4% of farms,  
71 respectively, in Slovakia (n=27; Čerňanská and others 2006), and benzimidazole and levamisole  
72 resistance on 83% and 50%, respectively, of farms in Western France (n=23; Chartier and others  
73 1998). In the latter study, benzimidazole resistance was also detected on 93% of goat farms (n=15).  
74 A further random survey of dairy goat farms in Southwestern France detected benzimidazole  
75 resistance on 83% of farms, and multiple resistance to benzimidazole and levamisole on 11% of  
76 farms (n=18; Chartier and others 2001). A sample size-weighted mean prevalence of benzimidazole  
77 resistance in GINs in sheep and goats of 50.1% was estimated from the above four studies. Excluding  
78 goats, the sample size-weighted mean prevalence of benzimidazole resistance in sheep GINs was  
79 32.1%. Insufficient data were available to estimate mean prevalence for other anthelmintic classes  
80 and cattle. The prevalence of AR has also been estimated elsewhere e.g. treatment failure has been  
81 identified on 51% of Irish sheep farms surveyed (Keane and others 2014) and 64% of Scottish sheep  
82 farms surveyed (Bartley and others 2003). These studies provide valuable prevalence estimates but  
83 differences in sample (farm) selection methods introduce potential sample selection bias and may  
84 affect estimates and comparability between regions. For example, Domke and others (2012a)  
85 observed AR on 33% of randomly selected sheep flocks and 80% of non-randomly selected sheep  
86 flocks in the Rogaland region of Norway. Therefore, it is recommended that future prevalence  
87 surveys follow a random or stratified sampling approach where possible to reduce sample selection  
88 bias.

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

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

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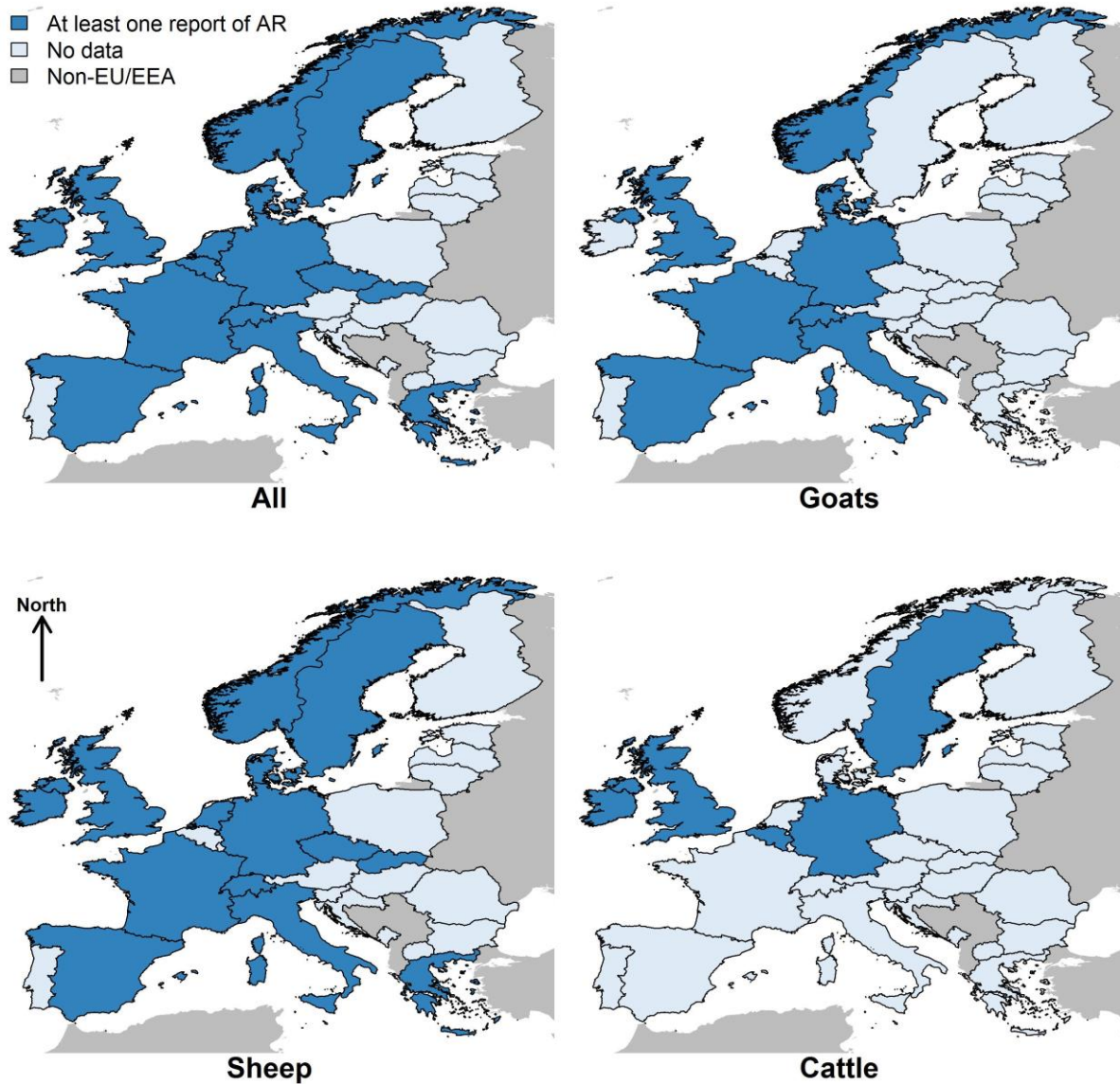
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- 336

337 **Supplementary figure.** The distribution of reported cases of anthelmintic resistance (AR) in the  
338 European Union, European Economic Area and Switzerland, at national level, based on the  
339 systematic review. Shaded countries had at least one reported case of AR. Note that regional  
340 distribution within countries is not plotted: see supplementary table for details of drug classes and  
341 GIN genera/species, and individual references for specific locations and apparent prevalence. No  
342 data were available for Iceland (not shown).



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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 <sup>a</sup>	Host	Region	References
<i>Teladorsagia</i> 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 <sup>b</sup> , 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

<b>MDR</b>	<b>Sheep</b>	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
	<b>Goats</b>	Denmark, France, UK	Chartier and others 2001, Jackson and others 1992, Maingi and others 1996a

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***Trichostrongylus spp.***

<b>BZ</b>	<b>Sheep</b>	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
	<b>Goats</b>	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
<b>ML</b>	<b>Sheep</b>	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
	<b>Goats</b>	Denmark, Italy, Switzerland	Artho and others 2007, Maingi and others 1996a, Murri and others 2014, Zanzani and others 2014
<b>LEV</b>	<b>Sheep</b>	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
	<b>Goats</b>	Denmark, France	Chartier and others 2001, Maingi and others 1996a, Paraud and others 2009

<b>MDR</b>	<b>Sheep</b>	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
	<b>Goats</b>	Denmark, France	Chartier and others 2001, Maingi and others 1996a

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***Haemonchus contortus***

<b>BZ</b>	<b>Sheep</b>	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
	<b>Goats</b>	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
<b>ML</b>	<b>Sheep</b>	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
	<b>Goats</b>	Germany, Switzerland	Artho and others 2007, Murri and others 2014, Scheuerle and others 2009, Schnyder and others 2005
<b>LEV</b>	<b>Sheep</b>	Greece, Netherlands	Borgsteede and others 1997, Geurden and others 2014
	<b>Goats</b>	France	Chartier and others 2001
<b>MDR</b>	<b>Sheep</b>	Greece, Netherlands	Borgsteede and others 1997, Geurden and others 2014, Van den Brom and others 2013
	<b>Goats</b>	France, Switzerland	Chartier and others 2001, Schnyder and others 2005

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***Ostertagia ostertagi***

<b>BZ</b>	<b>Cattle</b>	Belgium <sup>b</sup>	Borgsteede and others 1992
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<b>ML</b>	<b>Cattle</b>	Germany, Sweden	Demeler and others 2009
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***Cooperia oncophora***

<b>ML</b>	<b>Cattle</b>	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
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**Other<sup>c</sup>**

<b>BZ</b>	<b>Sheep</b>	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
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<b>LEV</b>	<b>Sheep</b>	Ireland, UK	Burgess and others 2012, Grimshaw and others 1994, Keane and others 2014
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<b>ML</b>	<b>Sheep</b>	Ireland	Keane and others 2014
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<b>MDR</b>	<b>Sheep</b>	UK	Burgess and others 2012
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<sup>a</sup>AH = anthelmintic, BZ = benzimidazoles (including pro-BZs), ML = macrocyclic lactones, LEV = levamisole, MDR = multiple drug resistance

<sup>b</sup>Suspected resistance

<sup>c</sup>Other minor species, or species/genera not identified