

Antimicrobial & antiparasitic use and resistance in British sheep and cattle: a systematic review

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1 Antimicrobial & antiparasitic use and resistance in British sheep and 2 cattle production systems: a systematic review

3

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11

12 Abstract

13 A variety of antimicrobials and antiparasitics are used to treat British cattle and sheep to
14 ensure animal welfare, a safe food supply, and maintain farm incomes. However, with
15 increasing global concern about antimicrobial resistance in human and animal populations,
16 there is increased scrutiny of the use of antimicrobials in food-producing animals.

17 This systematic review sought to identify and describe peer and non-peer reviewed sources,
18 published over the last ten years, detailing the usage of, and resistance to, antimicrobials
19 and antiparasitics in sheep and cattle farming systems in Britain as well as identify
20 knowledge gaps. Applying the PRISMA review protocol and guidelines for including grey
21 literature; Scopus, Web of Science, Medline, and government repositories were searched
22 for relevant articles and reports. Seven hundred and seventy titles and abstracts and 126
23 full-text records were assessed, of which 40 scholarly articles and five government reports
24 were included for data extraction.

25 Antibiotic usage in sheep and cattle in Britain appear to be below the UK average for all
26 livestock and tetracyclines and beta-lactam antibiotics were found to be the most
27 commonly used. However, the poor level of coverage afforded to these species compared
28 to other livestock reduced the certainty of these findings. Although resistance to some

29 antibiotics (using *Escherichia coli* as a marker) appears to have decreased in sheep and cattle
30 in England and Wales over the last few years, levels of resistance remain high to the
31 commonly used antibiotics. The small number and fragmented nature of studies identified
32 by this review describing anthelmintic usage, and the lack of available national sales data,
33 prevented the identification of trends in either sheep or cattle.

34 We recommend that additional efforts are taken to collect farm or veterinary level data on
35 antimicrobial usage and resistance, especially in sheep, which appear from this review to be
36 a neglected species in this field. Additionally, metrics produced by this data should be
37 generated in a way to allow for maximum comparability across species, sectors, and
38 countries.

39
40

41 Introduction

42 The use of antimicrobial and antiparasitic agents allow the control of pathogens in order to
43 increase animal health, welfare, and productivity in livestock settings which are challenged
44 by disease (Page and Gautier 2012). However, the increased use of these agents over the
45 last 70 years has led to the development of resistance to treatment with subsequent
46 negative health and economic effects (Heymann 2006). Antimicrobial resistance is
47 recognised as a global health threat, and is predicted to develop into a leading cause of
48 human fatality by 2050, with an annual cost to the global economy of 100 trillion US dollars
49 (O'Neill 2016). Anthelmintic resistance while primarily species specific, is a major cause of
50 poor productivity and economic loss in livestock production systems globally (Shalaby 2013).

51 While the interactions between human, animal, and environmental microbiomes are
52 complex and not fully understood, evidence exists linking the use of antibiotics in one
53 microbiome to the prevalence of resistant organisms in another; occupational exposure to
54 livestock has been reported as a risk for human health, particularly among veterinarians,
55 farmers, livestock cullers, and slaughterhouse workers, who are exposed to organisms such
56 as livestock associated methicillin resistant *Staphylococcus aureus* (MRSA) and *Coxiella*
57 *burnetii* (Klous *et al.* 2016; Rossi *et al.* 2017; Tang *et al.* 2017). While reducing the use of
58 antimicrobials in one population is known to be correlated with a reduction in resistance in
59 the same population, evidence linking reductions of use in livestock with reductions of

60 resistant organisms in humans is currently scarce (Dorado-García *et al.* 2016; Tang *et al.*
61 2017; Træholt Franck *et al.* 2017; Veldman *et al.* 2017; Bennani *et al.* 2020). Thus, while
62 measures to reduce antimicrobial usage in farming provide safeguarding mechanisms to
63 protect their therapeutic use in livestock, delineating the benefit such measures have to
64 protect the therapeutic use of antimicrobials in humans remains challenging.

65 Although there are calls to govern the use of antimicrobials at an international level
66 (Woolhouse *et al.* 2015; Padiyara *et al.* 2018), with guidance documents and action plans
67 from global bodies such as the World Health Organisation (WHO), Food and Agriculture
68 Organisation (FAO), and the World Organisation for Animal Health (OIE), (FAO 2016; OIE
69 2016; WHO 2019), there is no legally binding international treaty (no Montreal or Kyoto
70 protocol) on how they should be used or documented (Heymann and Ross 2019). At a
71 national level, there are various best practice guidelines available to antimicrobial and
72 antiparasitic users in livestock in Britain, such as the UK government's One Health report on
73 antibiotic use and resistance (VMD 2019a) and five-year action plan for antimicrobial
74 resistance (DHSC 2019), the British Veterinary Association's policy statement on the
75 responsible use of antimicrobials in food producing animals (BVA 2019), and the industry led
76 initiatives Sustainable Control of Parasites in Sheep (SCOPS 2019) and Control of Worms
77 Sustainably (COWS 2019a). To date, the use of antimicrobials in livestock in Britain is
78 governed by EU (indirectly) and national legislation, which include the 2006 ban on
79 antibiotics being used as growth promoters and a 2018 proposal to restrict the routine use
80 of prophylactic and metaphylactic antibiotics (due to come into effect in 2022) (European
81 Parliament 2019). Although possible to repeal EU legislation post-Brexit, it is likely the UK
82 will adopt this legislation after its exit as the UK has been one of the forerunners of effective
83 voluntary strategies to reduce antimicrobial use driven by strong private-public partnerships
84 and private industry involvement and leadership.

85 In Britain, the Veterinary Medicines Directorate (VMD; an agency of the Department of
86 Environment Farming and Rural Affairs) regulates medicine registration and use. The
87 National Office of Animal Health (NOAH) and the Responsible Use of Medicines in
88 Agriculture Alliance (RUMA), two industry initiatives, set the background of what
89 antimicrobials are available and how they are used in livestock. And yet, apart from pigs and
90 poultry, the level of use of antimicrobials in British livestock production is relatively

91 unknown at farm level. Often, due to multi-species registration of medicines, amounts of
92 antimicrobials are stated at livestock level and not species or farm level. Although farmers
93 are legally required to record the amount of antimicrobials they have used (DEFRA 2019),
94 this data is used for individual farm management and farm assurance schemes, and not
95 stored in a central database and therefore not readily available for antimicrobial usage
96 surveillance.

97 Usage of antibiotics is calculated through national sales data by the VMD, and while this
98 inferred usage has good coverage for some livestock species (for example usage in salmon
99 farming is 100% complete), there is only 30% coverage for dairy cattle, 5.5% coverage for
100 beef cattle, and no known sales data coverage for sheep (VMD 2018). Additionally, as
101 antimicrobials are often registered to multiple livestock species, sales cannot be reliably
102 related to a certain species, unless the drug of use is solely registered to said species (for
103 example products solely licensed to fish). The VMD collects antibiotic sales data and usage
104 data. Antibiotic sales data are submitted by pharmaceutical companies to the VMD on their
105 previous year's sales of antimicrobials authorised for use in animals in accordance with
106 veterinary medicine regulations 2013. Antibiotic usage data are collected and submitted
107 voluntarily by different livestock stakeholders to the VMD. This was the result of a
108 collaboration between RUMA and the VMD and first published in 2014 with only usage data
109 from the poultry sector until more data became available in the subsequent years.
110 Additionally, although the UK participates in mandatory EU-wide antibiotic resistance
111 monitoring, in 2018 samples were only taken from poultry (VMD 2018), and so
112 understanding the links between antimicrobial usage and resistance at the animal and farm
113 level is challenging.

114 Cattle and sheep are the two most commonly produced red meat species in Britain and
115 understanding the level of usage and resistance of/to anti-infective agents is an important
116 aspect of the national agenda for controlling antimicrobial resistance and ensuring the
117 sustainability of domestic meat production, especially given the changing horizon ahead by
118 leaving the governance of the EU behind. Consequently, the aim of this study was to
119 conduct a systematic review on the use and resistance of antimicrobials and antiparasitics in
120 cattle and sheep production systems in Britain to provide an overview of the current
121 situation and identify gaps in knowledge.

122

123 Methods

124 Search strategy

125 A systematic literature review was conducted in line with PRISMA guidelines (Moher *et al.*
126 2015). First, an *a priori* protocol was produced which set out the primary and secondary
127 objectives and the review question; namely to (1) identify and describe the existing
128 literature detailing the level of usage and resistance to antimicrobials and antiparasitics in
129 British¹ sheep and cattle production systems, and (2) identify any research gaps within this
130 topic. Inclusion criteria were defined based on the *population, intervention, comparison,*
131 *outcomes* of an article, and *study* design framework (PICOS, adapted from Chatterjee *et al.*,
132 (2018)) and included; English language, peer-reviewed texts and reports, which had a focus
133 on sheep and/or cattle raised for meat production in Britain (England, Wales, and Scotland)
134 published in the last ten years; further details are given in Supp. 1 (section 6). The search
135 was conducted on the 11th and 12th June 2019 in Scopus, Web of Science and Medline
136 databases. These three databases were selected to provide a high level of article recall
137 across biomedical articles (Bramer *et al.* 2017).

138 Search terms were derived using the Boolean operator OR for the following four themes, (1)
139 anti-infective agent, (2) livestock population², (3) location, and (4) focus, before being
140 combined using the Boolean operators 'AND' and 'AND NOT' (Table 1). The term 'UK or
141 United Kingdom' was included at this stage to screen for any articles which may contain
142 information on England, Scotland, or Wales.

143 Table 1. Search terms used to build the systematic review

Anti-infective agent	Livestock population	Location	Focus	Exclude
(antimicrobial* OR "anti microbial*" OR antibiotic* OR "anti biotic*" OR	AND (livestock OR cattle OR beef OR cow OR cows OR calf OR calv* OR	AND (GB OR "Great Britain" OR England OR English OR wales OR welsh	AND (use OR using OR usage OR resis* OR	AND NOT "New south wales"

¹ British (English, Scottish, and Welsh) production systems were the focus of this review (rather than the whole of the United Kingdom)

² As around half of British beef is supplied from the dairy sector (through calves and cull cows) (AHDB 2017) the use of antibiotics in dairy cows was considered a relevant indicator of antibiotic use in red meat production.

antifungal* OR “anti fungal*” OR antiprotozoal* OR “anti protozoal*” OR bactericid* OR bacteriostat* OR anti- infective* OR “anti infective*” OR antiviral* OR “anti viral*” OR vermifuge* OR antiparasitic* OR “anti parasitic*” OR anthelmintic* OR antihelmintic* or wormer)	heifer* OR bull OR bulls OR bovine OR sheep OR lamb* OR ewe OR ewes OR ram OR rams OR ovine OR dairy)	OR Scotland OR Scottish OR UK OR “united kingdom”)	treatment* OR incidence OR prevalence OR risk OR “risk factor” OR driver)
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144

145 To complement the search in scientific databases and achieve a complete systematic
 146 review, grey literature was searched using the methodology described by Mahood *et al.*
 147 (2014) to screen for data sets and reports. Rather than using open search engines (e.g.
 148 Google.com) which may result in unreliable sources, we targeted government data sets
 149 (Piasecki *et al.* 2018). The UK’s government’s data repositories³ were searched using the
 150 same search terms and parameters as described in Table 1. The only difference is that the
 151 government search function is not as sophisticated; only using the Boolean operator ‘AND’.

152

153 **Relevance screening and full text appraisal**

154 After duplicate removal, two reviewers (MH and LW) independently reviewed the same 10%
 155 of the articles (n=69), selected by random using a random number generator in Excel, by
 156 title and abstract using the PICOS inclusion criteria. Once both reviewers had screened the
 157 sample articles, the conclusion on whether to include or exclude were compared in order to
 158 measure the inter-rater reliability using observed proportional agreement and Cohen’s
 159 kappa, calculated manually using the method described by Cohen (1960) (Supp. 1; part 8).
 160 Observed proportional agreement between the two observers was 91.3%, with a
 161 corresponding Cohen’s kappa of 0.812 indicating strong level inter-rater reliability IRR. The
 162 reviewers discussed the six articles on which they disagreed in order to reach a consensus

³ <https://www.gov.uk/search/research-and-statistics>

163 and to clarify the screening criteria. Given the high level of IRR, it was deemed acceptable to
164 allow a single reviewer (MH) to screen the remaining articles and apply inclusion and
165 exclusion criteria. Full text appraisal of the remaining articles was completed by two
166 independent reviewers (MH and LW). Grey literature records were screened for relevance
167 using the same PICOS inclusion criteria. During the review process citation lists were
168 examined to check recall accuracy and to identify possible additional articles for inclusion in
169 the review.

170 Data extraction

171 Data was extracted from both the included scientific articles and reports into Microsoft
172 Excel (version 16.33); capturing data on the target population, area of interest, geographic
173 location, study design, and outcome indicators (such as the number of farms using
174 antimicrobials, percentage of bacterial isolates resistant to antibiotics, or proportion of
175 farms with anthelmintic resistance) (a summary of which is presented in Supp. 2). Where
176 reports contained disaggregated data (such as antibiotic resistance profiles by species,
177 region, and year), this data was extracted and collated to allow visualisation of trends.
178 Where sources contained data relating to the United Kingdom, rather than Britain (the focus
179 of this review), data was disaggregated into constituent countries.

180

181 Results

182 Summary of articles

183 A total of 773 articles were screened for this review: 687 primary articles identified through
184 searching Scopus, Web of Science, and Medline, 83 documents and reports identified
185 through a grey literature search, and 3 additional articles identified by examining the
186 citation lists of these primary articles. All articles were written in English; no exclusion of
187 articles was done based on language.

188

189 **Figure 1.** Flow chart documenting literature retrieval and criteria used to select articles and reports for
190 inclusion in the systematic review of anti-infective agents in sheep and cattle populations in Britain.

191

192 Descriptive statistics of selected articles and reports

193 Of the final 40 articles half focused solely on cattle, 19 focused solely on sheep, and one
194 article contained data on both species. Most articles (29/40) contained data on resistance to
195 anti-infective agents while fewer articles (15/40) contained data on the usage of anti-
196 infective agents (Table 2). Four articles contained data relating to more than one area of
197 interest.

198 Table 2. Topic areas covered in articles

Area of interest	Number of articles	% of articles
Antibiotic usage	10	25
Antibiotic resistance	16	40
Anthelmintic usage	6	15
Anthelmintic resistance	12	30
Anti-ectoparasitic resistance	2	5

199 *NB. Total number of articles and reports exceeds 40 as some records contained data on more than one area of interest*

200 The grey literature reports included two relevant data series; annual data for Veterinary
201 Antimicrobial Resistance and Sales Surveillance (VARSS) published by the Veterinary
202 Medicines Directorate (VMD) in 2013, 2015 and 2018, and reports on antibiotic usage from
203 the task force for Responsible Use of Medicines in Agriculture (RUMA) published in 2018
204 and 2019.

205 A total of 36 articles (90%) covered population data from England, 25 (62.5%) from Wales,
206 and 20 (50%) from Scotland (total number of articles exceeds 40 as many articles contained
207 data on more than one country).

208 *Antibiotic use*

209 Antibiotic usage was detailed in the results of nine (23%) of the articles (five focused on
210 cattle and four focused on sheep) (Table 3). Seven of the nine articles (78%) targeted
211 farmers for data collection using a questionnaire-based approach and in the remaining two
212 veterinary sales data were used.

213 The five reports used antibiotic sales data collected from veterinary practices and
214 pharmaceutical companies as part of nationwide antibiotic use surveillance. For cattle, data
215 on antibiotic usage were reported by RUMA and the VMD over a four- and five-year period,
216 respectively. The RUMA reports use benchmark values for antibiotic usage in dairy cattle
217 provided by two groups of dairy farms from Kite Consulting and Solway Vets (n=674) and

218 from Kingshay consultants (n=409). The 2019 RUMA report contained information on 3,458
 219 beef farms (representing 5.5% of British production) and 2,978 dairy farms (30% of the
 220 national herd) collected from veterinary practice sales data by FarmVet Systems⁴. For sheep,
 221 the reports contained information on antibiotic usage from a single study by Davies *et al.*
 222 (2017) already included in this review.

223 Table 3. Studies on antibiotic usage
 224

Study	Population	Location	Random sampling	Sample size (farms)	Method of data collection
Rutherford et al., 2015	Sheep	EN, WA	No	19	Questionnaire
Davies et al., 2017	Sheep	EN, SC, WA	No	207	Practice sales data
O’Kane et al., 2017	Sheep	EN	Yes	1294	Questionnaire
Lima et al., 2019	Sheep	EN, SC, WA	No	648	Questionnaire
Brunton et al., 2012	Cattle	EN, WA	Yes	557	Questionnaire
Horseman et al., 2013	Cattle	EN, SC, WA	Yes	84	Questionnaire
Hyde et al., 2017	Cattle	EN	No	332	Practice sales data
Fujiwara et al., 2018	Cattle	EN, WA, SC	No	148	Questionnaire
Higham et al., 2018	Cattle	EN, WA, SC	No	372	Questionnaire

225 EN = England, SC = Scotland, WA = Wales

226 The majority of the studies produced a proportional outcome metric related to a particular
 227 farming practice (for example; the % of farmers using antibiotics to treat lameness). Two
 228 studies used practice sales data and details of farm flock and herd compositions to generate
 229 estimates of antibiotic use in milligrams per population corrected unit (mg/PCU), defined
 230 daily doses vet (DDDvet), and defined course doses vet (DCDvet).

231 **Antibiotic usage in sheep**

232 The three studies looking at antibiotic usage in sheep from farm level data described usage
 233 regarding the treatment of footrot (one of the lead causes of lameness in sheep) and new
 234 born lambs; the proportion of farmers using antibiotic injections to treat footrot was found
 235 to be 24.4% (O’Kane *et al.* 2017), and the proportion of farmers administering prophylactic
 236 antibiotics to new born lambs was 26.8% in a general population of sheep farms (Lima et al.,
 237 2019) and 73.7% in a population of sheep farms which reported to have joint ill present
 238 (Rutherford et al., 2015).

⁴ FarmVet Systems, provided by software company VetIMPRESS; www.vetimpress.com

239 In the study by Davies *et al.* (2017) which looked at antibiotic use in 207 sheep farms,
 240 antibiotic usage was found to have a mean mg/PCU of 11.38 (s.d. 15.35, range 0-116.9),
 241 1.47 DDDvet (s.d. 2.1), and 0.39 DCDvet per ewe per flock. The most common classes of
 242 antibiotics used were; tetracyclines (57.4%), penicillins (23.7%), and aminoglycosides
 243 (10.7%). Antibiotics were predominately administered parenterally (84.4% of the time).

244 **Antibiotic usage in cattle**

245 The five studies looking at antibiotic usage in cattle described the treatment of mastitis and
 246 lameness in dairy cattle. Mastitis was found to be the most common reason for the use of
 247 antibiotics (Higham *et al.*, 2018), with 93% of farmers using antibiotic intra-mammary tubes
 248 to treat mastitis during the lactation (Brunton *et al.*, 2012), and 96% of farmers using
 249 antibiotic dry cow intra-mammary tubes (Fujiwara *et al.*, 2018). Regarding lameness
 250 treatment (sole ulcer, sole bruising, and white line disease) 55% of farmers reported using
 251 injectable antibiotics as an option to treat clinical cases (Horseman *et al.*, 2013).

252 In the study by Hyde *et al.* (2017) on 332 dairy farms, antibiotic usage was found to have a
 253 mean mg/PCU of 22.11 (range 0.36-97.79), 4.22 DDDvet (range 0.05-20.29), and 1.93
 254 DCDvet (range 0.01-6.74). The most common type of antibiotics used were beta-lactams
 255 and aminoglycosides which comprised 42.8% and 20.9% respectively. Parenteral treatment
 256 was the most common route of administration (78.1% of the time).

257 The VMD and RUMA reports contained antibiotic consumption data from 2014-2018 for
 258 dairy and beef production systems and are shown in tables 4 and 5.

259 Table 4. Antibiotic usage in cattle by class (VMD 2019b)

Antibiotic	Beef mg/kg (%)	% change 2017-2018	Dairy mg/kg (%)	% change 2017-2018
Penicillin and 1 st generation cephalosporins	5.0 (24)	+28	5.5 (32)	+8
Tetracyclines	7.3 (35)	-16	3.2 (19)	+14
Aminoglycosides	3.8 (18)	+31	3.5 (20)	+13
Macrolides	1.7 (8)	+13	1.9 (11)	-2
Trimethoprim/sulphonamides	1.3 (6)	+30	1.9 (11)	+20

260

261 Table 5. Antibiotic usage in beef and dairy cattle (RUMA 2019; VMD 2019b)

	Baseline (2016) ⁵	2017-2018	2018-2019	% change compared to baseline
Total usage (mg/kg)				
<i>FarmVet Systems</i>				
Beef	-	19	21	
Dairy	26.2	16	17	-29.2
<i>Kite consultants & Solway Vets</i>				
Dairy	26.2	23.7	21.9	-16.4
<i>Kingshay consultants</i>				
Dairy	26.2	20.5	17.3	-34.0
Intramammary tubes (DCDVet)				
<i>UK-VARSS</i>				
Dry cow	0.732	0.547	0.644	-12
Lactating cow	0.808	0.694	0.776	-4
<i>Kite consultants & Solway Vets</i>				
Dry cow	0.732	0.5	0.46	-37
Lactating cow	0.808	0.66	0.55	-32
<i>Kingshay consultants</i>				
Dry cow	0.732	0.522	0.519	-29
Lactating cow	0.808	0.801	0.601	-26

262

263 *Antibiotic resistance*

264 Of the 40 articles, 16 contained information about antibiotic resistance; 12 (75%) about
265 resistance in cattle, three (19%) in sheep and one of the studies contained information
266 about both cattle and sheep (6%) (Table 6).

267 Nine of the studies (56%) conducted bacterial identification and resistance testing from
268 samples collected from farms (e.g. from bulk milk tanks or clinical cases) while the
269 remaining seven studies (44%) analysed pre-existing laboratory data. From the 16 studies,
270 eight (50%) focused on *Enterobacteriaceae* species with *Escherichia coli* (*E. coli*) being the
271 most common organism profiled, followed by *Staphylococcus aureus* (*S. aureus*) in 4/16
272 (25%). Two studies (13%) used a form of random sampling in their study design.

273

274 Table 6. Studies on antibiotic resistance

275

Study	Population	Location	Random sampling	Sample size	Source of samples	Organism
Wu et al., 2014	Sheep	EN, SC, WA	No	41	Pre-existing laboratory samples	<i>Campylobacter jejuni</i>

⁵ Baseline data taken from a single source; FarmVet Systems

Rutherford et al., 2015	Sheep	EN, WA	No	25	On farm sampling (sheep with joint ill)	<i>Streptococcus dysgalactiae</i>
Angell et al., 2015	Sheep	EN, WA	No	20	On farm sampling (sheep with CODD lesions)	<i>Treponema spp.</i>
Cheney et al., 2015	Sheep	EN, WA	No	101	Pre-existing laboratory samples	<i>Escherichia coli</i>
García-Álvarez et al., 2011	Cattle	EN	No	940	Pre-existing laboratory samples	<i>Staphylococcus aureus</i>
Warner et al., 2011	Cattle	EN, WA	No	65	On farm sampling (<i>not stated from where</i>)	<i>Escherichia coli</i>
Wu et al., 2012	Cattle	EN, WA	No	34	Pre-existing laboratory samples	<i>Escherichia coli</i>
Paterson et al., 2012	Cattle	EN, SC, WA	No	1500	On farm sampling (bulk milk tank)	<i>Staphylococcus aureus</i>
Randall et al., 2014	Cattle	EN, WA	Yes	103	On farm sampling (waste milk samples)	<i>Enterobacteriaceae</i>
Ayling et al., 2014	Cattle	EN, SC, WA	No	45	Pre-existing laboratory samples	<i>Mycoplasma bovis</i>
Paterson et al., 2014	Cattle	EN, SC, WA	Yes	1090	On farm sampling (bulk milk samples)	<i>Staphylococcus aureus</i>
Cheney et al., 2015	Cattle	EN, WA	No	534	Pre-existing laboratory samples	<i>Escherichia coli</i>
Thomas et al., 2015	Cattle	EN, SC, WA	No	-	On farm sampling (mastitis cases)	<i>Escherichia coli</i> <i>Staphylococcus aureus</i> <i>Strep. uberis</i>
MacFadyen et al., 2018	Cattle	EN, WA	No	1100	On farm sampling (bulk milk samples)	<i>Macroccoccus caseolyticus</i>
Mellor et al., 2019	Cattle	EN, SC, WA	No	1115	Pre-existing laboratory samples	<i>Salmonella typhimurium</i>
Mueller-Doblies et al., 2018	Cattle	EN, SC, WA	No	45,336	Pre-existing laboratory samples	<i>Salmonella typhimurium</i>
Velasova et al., 2019	Cattle	EN, SC, WA	No	40	On farm sampling (faecal samples)	<i>Enterobacteriaceae</i>

NB. EN = England, SC = Scotland, WA = Wales

276

277 The 2018 VARSS reports contained information on antibiotic resistance in both sheep and
278 cattle (as well as other animals) collated from samples sent to the Animal and Plant Health
279 Agency (APHA) laboratories for diagnostic purposes (VMD 2019b). Antibiotic resistance was
280 reported for the major livestock bacterial pathogens (such as species causing mastitis and
281 respiratory disease) as well as marker bacterial species significant to human health (such as
282 *E. coli* and *Salmonella spp.*) collected from livestock faecal samples (Table 7).

283 Table 7. Samples submitted to APHA included in the 2018 VARSS report (VMD 2019b)

Population	Location	Sample size	Organism	Data range available
Sheep	UK	22	<i>Streptococcus dysgalactiae</i>	2011-2018

Sheep	UK	81	<i>Mannheimia haemolytica</i>	2011-2018
Sheep	UK	50	<i>Biberstein trehalosi</i>	2011-2018
Sheep	EN, WA	72-161	<i>Escherichia coli</i>	2013-2018
	SC	67		
Sheep	EN, WA	276	<i>Salmonella spp.</i>	2013-2018
	SC	68		
Cattle	UK	110	<i>Escherichia coli</i>	2011-2018
Cattle	UK	32	<i>Streptococcus dysgalactiae</i>	2011-2018
Cattle	UK	84	<i>Streptococcus uberis</i>	2011-2018
Cattle	UK	36	<i>Staphylococcus aureus</i>	2011-2018
Cattle	UK	76	<i>Pasteurella multocida</i>	2011-2018
Cattle	UK	44	<i>Mannheimia haemolytica</i>	2011-2018
Cattle	EN+WA	208	<i>Escherichia coli</i>	2013-2018
	SC	157-313		
Cattle	EN+WA	489	<i>Salmonella spp.</i>	2013-2018
	SC	140		

NB. EN = England, SC = Scotland, WA = Wales, UK = United Kingdom

284

285 **Antibiotic resistance in sheep**

286 The four studies investigating antibiotic resistance in sheep reported on four different
287 organisms; *E.coli*, *Campylobacter jejuni* (*C. jejuni*), *Streptococcus dysgalactiae* (*S.*
288 *dysgalactiae*), and *Treponema* species. In their study of antibiotic resistance of *E. coli* from
289 diseased farm livestock, Cheney et al. (2015), found that 57.4% of non-verotoxigenic *E. coli*
290 were resistant to at least one antimicrobial and the highest level of resistance for
291 tetracycline (56.4% of isolates), sulphonamides (48.5%), ampicillin (37.6%), and
292 streptomycin (31.7%). A study of abortion associated with *C. jejuni* by Wu et al. (2014) found
293 that of the 42 isolates, 17.1% were resistant to nalidixic acid, 9.8% resistant to clindamycin,
294 4.9% resistant to tetracyclines, and 2.4% resistant to azithromycin (the authors did not state
295 what percentage of isolates were resistant to at least one antimicrobial). In a study of *S.*
296 *dysgalactiae* isolated from sheep with joint ill, Rutherford et al. (2015) reported that all 25
297 isolates were resistant to tetracycline. Angell et al. (2015) tested the in-vitro susceptibility of
298 contagious ovine digital dermatitis associated *Treponema* species and found that all 20
299 isolates were susceptible to ten different antibiotics.

300 The VARSS 2018 report showed high a level of resistance to tetracyclines in *S. dysgalactiae*
301 and *Mannheimia haemolytica* (Table 8; VARSS 2018).

302 Table 8. Antibiotic resistance in major sheep pathogens taken from VARSS 2018 report

Resistant isolates (%)								
	Number of isolates	Ampicillin	Amoxicillin/ clavulanate	Enrofloxacin	Trimethoprim	Tetracycline	Neomycin	Tylosin
Common mastitis pathogens: <i>Streptococcus dysgalactiae</i>	22	0	0			77.3		0
Common respiratory pathogens: <i>Mannheimia haemolytica</i>	81	2.5	0	0	0	46.9		
<i>Bibersteinia trehalosi</i>	50	0	0	0	0	2.0		

NB. In sheep, *Mannheimia haemolytica* can also cause mastitis

303

304 High levels of antibiotic resistance were reported in isolates of *E. coli* from sheep in England,
 305 Wales, and Scotland, with the highest levels detected to tetracycline, ampicillin, and
 306 spectinomycin in all countries, streptomycin in England and Wales, and
 307 amoxicillin/clavulanate in Scotland (Figure 2; VARSS 2013-2018). Levels of resistance were
 308 found to be decreasing in *E. coli* in sheep in England and Wales, while levels of resistance in
 309 sheep in Scotland showed an increase over the last two years.

310 **Figure 2.** Percentage of *E. coli* isolates from sheep resistant to different antibiotics in (A) England and Wales,
 311 and (B) Scotland

312

313 In 2018, the highest level of resistance in *Salmonella spp.* from sheep in England and Wales
 314 was to streptomycin (7.6% of isolates), and in Scotland was to sulphonamide compounds
 315 (11.8% of isolates) (Figure 3; VARSS 2013-2018).

316 **Figure 3.** Percentage of *Salmonella* isolates from sheep resistant to different antibiotics in (A) England and
 317 Wales, and (B) Scotland

318

319 Antibiotic resistance in cattle

320 Four studies reported on the resistance profiles to *S. aureus*; two examining isolates from
 321 mastitis cases and two examining isolates from bulk milk samples. Thomas et al., (2015)
 322 found that of the 38 *S. aureus* isolates from mastitis cases, 31.6% were resistant to penicillin
 323 G, and García-Álvarez et al., (2011) found that of the 940 *S. aureus* isolates from mastitis
 324 cases, 2.6% were resistant to methicillin, though none were positive for the *mecA* gene

325 (used to confirm methicillin-resistant *S. aureus* [MRSA]). Paterson et al. (2012) identified 300
 326 MRSA isolates from 1500 bulk milk samples and found that seven of the isolates (originating
 327 from five geographically remote locations) were *mecA* positive and belonged to the clonal
 328 complex CC398. Another study from the same author documented the presence of *mecC*
 329 MRSA in ten out of 375 (2.7%) English farms and one sample of *mecA* MRSA (Paterson et al.,
 330 2014).

331 Three articles described three miscellaneous bacteria; *Mycoplasma bovis*, *Streptococcus*
 332 *uberis* (*S. uberis*), and *Macrococcus caseolyticus*. Ayling et al., (2014) reported that
 333 *Mycoplasma bovis* had shown increasing levels of resistance over a five-year period
 334 (between 2004 and 2009), demonstrated by rising MIC50 levels, though as minimum
 335 inhibitory concentrations to define resistance have not been set for this bacterium the
 336 prevalence of resistance could not be stated. Thomas et al., (2015) reported that in 39
 337 isolates of *S. uberis*, 12.8% and 7.7% were resistant to tetracycline and erythromycin
 338 respectively. In their study of *Macrococcus caseolyticus*, MacFayden et al., (2018) found that
 339 all the 33 isolates grown from bulk milk tanks were positive for *mecB* and *mecD*.

340 Studies which investigated *Enterobacteriaceae* species included those which looked for
 341 extended spectrum beta lactamase (ESBL) markers in various bacteria and those which
 342 reported on resistance in specific bacterial species (Table 9).

343 Table 9. Antibiotic resistance in *Enterobacteriaceae* species

Study	Source of samples	Resistance
Randall et al., 2014	Waste milk samples (n=103)	6.8% samples positive for ESBL
Velasova et al., 2019	Faecal samples (n=40)	25% samples positive for ESBL
Warner et al., 2011	On farm sampling (n=65)	ESBL <i>E. coli</i> found on 43.1% of farms
Cheney et al., 2015	Pre-existing lab samples (n=534)	84.1% non-VTEC <i>E. coli</i> resistant to at least one antibiotic 56.5% VTEC <i>E. coli</i> resistant to at least one antibiotic
Wu et al., 2012	Pre-existing lab samples (n=34)	61.7% of <i>E. coli</i> with at least one antibiotic resistant gene
Mueller-Doblies et al., 2018	Pre-existing lab samples (n=244)	69.2% of <i>Salmonella</i> isolates resistant to one of more antibiotics
Mellor et al., 2019	Pre-existing lab samples (n=1115)	85.4% of <i>Salmonella</i> isolates resistant to one of more antibiotics 74.7% of <i>Salmonella</i> isolates resistant to three or more antibiotics

ESBL= Extended spectrum beta lactamase; *E. coli* = *Escherichia coli*; VTEC= Verotoxigenic *E. coli*

345 Cheney et al. (2015), found high levels of resistance in *E. coli* to sulphonamides (73.6% of
 346 isolates), tetracycline (70.7% of isolates), ampicillin (69.5% of isolates), and streptomycin
 347 (48.5% of isolates). The VARSS 2018 report recorded a high level of resistance to
 348 tetracyclines in the following bacterial species: *S. dysgalactiae*, *Pasteurella multocida*, *S.*
 349 *uberis*, and *Mannheimia haemolytica* and a high level of resistance to neomycin in *S. uberis*
 350 (Table 10; VMD 2018).

351 Table 10. Antibiotic resistance in major cattle pathogens taken from VARSS 2018 report

	Number of isolates	Resistant isolates (%)						
		Ampicillin	Amoxicillin/ clavulanate	Enrofloxacin	Trimethoprim	Tetracycline	Neomycin	Tylosin
Common mastitis pathogens:								
<i>Escherichia coli</i>	110	21.8	5.5	2.7	6.4	13.6	2.7	
<i>Streptococcus dysgalactiae</i>	32	0	0			87.5	3.1	0
<i>Streptococcus uberis</i>	84	0	0			34.5	45.2	11.9
<i>Staphylococcus aureus</i>	36	27.8	0			2.8	0	2.8
Common respiratory pathogens:								
<i>Pasteurella multocida</i>	76	2.6	0	0	0	51.3		
<i>Mannheimia haemolytica</i>	44	2.3	0	0	0	50		

352

353 Overall the level of antibiotic resistance in *E. coli* reported was higher in cattle from England
 354 and Wales compared to Scotland. In all countries the highest levels of resistance were
 355 recorded to ampicillin and tetracycline. Resistance levels were found to be decreasing in *E.*
 356 *coli* from cattle in England and Wales. While resistance levels were also found to be
 357 decreasing in *E. coli* from cattle in Scotland from 2013 to 2017, resistance increased in 2018
 358 (Figure 4; VMD 2013-2018).

359 **Figure 4.** Percentage of *E. coli* isolates from cattle resistant to different antibiotics in (A) England and Wales,
 360 and (B) Scotland

361

362 In 2018 the highest level of resistance in *Salmonella spp.* from cattle in England and Wales
 363 was to streptomycin and sulphonamide compounds (both 13.9% of isolates), and in Scotland
 364 was to sulphonamide compounds (15.7% of isolates) (Figure 5; VMD 2013-2018).

365 **Figure 5.** Percentage of *Salmonella* isolates from cattle resistant to different antibiotics in (A) England and
 366 Wales, and (B) Scotland

367

368 *Anthelmintic use*

369 Of the 40 articles, six (15%) looked at anthelmintic usage; five in sheep and one in cattle
 370 (Table 11). All of the studies used farm level data to measure usage and was either captured
 371 by farmers self-reporting through questionnaires (n=5), or by ascertaining baseline usage
 372 levels before conducting trials into anthelmintic resistance (n=1). No reports were found
 373 reporting anthelmintic usage.

374 Anthelmintics are separated into five major groups; broad spectrum anthelmintics active
 375 against major species of helminths and some ectoparasites (groups 1-3); group 1-BZ
 376 (benzimidazoles), group 2-LV (imidazothiazoles, including levamisole), group 3-ML
 377 (macrocyclic-lactones), and newer generation anthelmintics (groups 4 & 5); group 4-AAD
 378 (amino-acetonitrile derivatives), and group 5-SI (spiro-indoles, such as derquantel, available
 379 as combination products) (Kaminsky *et al.* 2008; Little *et al.* 2011).

380 Table 11. Studies on anthelmintic usage

Study	Population	Location	Random sampling	Sample size (farms)	Method of data collection
Burgess et al., 2012	Sheep	EN, SC, WA	No	118	Questionnaire
Morgan et al., 2012	Sheep	EN, SC, WA	Yes	600	Questionnaire
Crilly et al., 2015	Sheep	SC	No	38	Questionnaire
Learmount et al., 2016	Sheep	EN, WA	No	14	Routine usage recorded as part of trial
Lima et al., 2019	Sheep	EN, SC, WA	No	615	Questionnaire
Bellet et al., 2018	Cattle	EN	No	43	Questionnaire

NB. EN = England, SC = Scotland, WA = Wales

381

382 **Anthelmintic use in sheep**

383 Of the six studies, two described the routine use of anthelmintics. In a study of 118 sheep
 384 farms, Burgess et al., (2012) reported that 99% of farmers gave treatment against
 385 nematodes and in a study of 600 farms, Morgan et al., (2012) reported that 93%, 67%, and
 386 58% of farmers routinely treated against nematodes, liver fluke, and tapeworms
 387 respectively. Two studies reported on specific farming practices; in their study of 615 sheep

388 farms, Lima *et al.* (2019) reported that farmers administered a group four or five
389 anthelmintic (monepantel and derquantel) to 32% and 28% of ewes and rams at quarantine.
390 Crilly *et al.*, (2015) reported that 27 out of 38 farmers (71%) used moxidectin (a macrocyclic
391 lactone) for the periparturient treatment of ewes. Macrocyclic lactones (group three
392 anthelmintics) were reported by three studies to be the most commonly used anthelmintic
393 against nematodes; 56% of 118 farms (Burgess *et al.*, 2012), 47% of 600 farms (Morgan *et al.*
394 *et al.*, 2012), and 84% (SCOPS farms⁶) and 70% (non SCOPS farms) in a study of 14 farms
395 (Learmount *et al.*, 2016). Benzimidazoles (group one anthelmintics) were reported to be
396 used against nematodes in 31% of 118 farms (Burgess *et al.* 2012), 26% of 600 farms
397 (Morgan *et al.*, 2012), and 7% (SCOPS farms) and 21% (non SCOPS farms) in a study of 14
398 farms (Learmount *et al.*, 2016). Levamisole (group two anthelmintics) had the lowest
399 reported use, ranging from 28-31% of 118 farms (Burgess *et al.*, 2012), 16% of 600 farms
400 (Morgan *et al.*, 2012), to 9% of 14 farms (Learmount *et al.*, 2016).

401 The mean number of times ewes were treated annually for nematodes (any class of
402 anthelmintic) was reported to be 2.0 (Burgess *et al.*, 2012), 2.35 (s.d. 1.48, range 0-12)
403 (Morgan *et al.*, 2012), and 2.4 (Learmount *et al.*, 2016). The mean number of times lambs
404 were treated for nematodes was reported to be 3.3 (Burgess *et al.*, 2012), 3.55 (s.d. 2.76,
405 range 0-16) (Morgan *et al.*, 2012), and 4.1 (Learmount *et al.*, 2016). Learmount *et al.*, (2016)
406 also reported that those farms following the SCOPS guidelines used significantly fewer
407 treatments in both ewes (ewes on SCOPS farms being treated between zero and three times
408 per year compared to non-SCOPS farms treating between zero and five times per year) and
409 lambs (lambs on SCOPS farms being treated between zero and five times per year compared
410 to non-SCOPS farms treating between zero and eight times per year), though it should be
411 noted that this study only contained seven SCOPS and seven non SCOPS farms.

412

413 **Anthelmintic usage in cattle**

414 Only one study, (Bellet *et al.*, 2018) consisting of 43 farms reported on the use of
415 anthelmintics in cattle and found that farmers routinely used anthelmintics on 85% and 44%

⁶ SCOPS – Sustainable Control of Parasites in Sheep (SCOPS 2019)

416 of their young stock and adult cows respectively. As with the sheep studies, the most
 417 common anthelmintic class used in young stock was macrocyclic lactones (89% of farms),
 418 which is consistent with the industry led cattle parasite guideline Control of Worms
 419 Sustainably (COWS) which recommend macrocyclic lactones as a first line treatment against
 420 the parasites *Ostertagia ostertagi* and *Cooperia oncophora* (COWS 2019b).

421

422 *Anthelmintic resistance*

423 Twelve of the 40 studies (30%) reported on anthelmintic resistance; ten in sheep and two in
 424 cattle (Table 12). No grey literature sources were found reporting anthelmintic resistance.

425 Faecal egg count reduction tests (FECRT) were used to test for resistance in the majority
 426 (n=9) of the studies; other tests for resistance were the larval development test (LDT) (n=4),
 427 egg hatch test (n=1), and farmer self-reported resistance (n=1).

428

429 Table 12. Studies on anthelmintic resistance

430

Study	Population	Location	Random sampling	Sample size (farms)	Method of resistance testing
Taylor et al., 2009	Sheep	EN, WA	No	40	FECRT & LDT
Mitchell et al., 2010	Sheep	WA	No	122	LDT
Burgess et al., 2012	Sheep	EN, SC, WA	No	118	Self-reported resistance
Jones et al., 2012	Sheep	EN, WA	No	11	FECRT
Daniel et al., 2012	Sheep	EN, SC, WA	No	25	FECRT
Stubbings and SCOPS, 2012	Sheep	EN, SC, WA	No	16	FECRT
Thomas, 2015	Sheep	WA	No	58	FECRT, LDT, EHT
Learmount et al., 2016a	Sheep	EN, WA	No	14	LDT
Glover et al., 2017	Sheep	EN	No	27	FECRT
Kamaludeen et al., 2019	Sheep	EN, WA	Partly	74	FECRT
McArthur et al., 2011	Cattle	SC	No	4	FECRT
Geurden et al., 2015	Cattle	EN, SC, WA	No	10	FECRT

EN = England, SC = Scotland, WA = Wales

FECRT = Faecal egg count reduction test, LDT = Larval development test, EHT = Egg hatch test

431

432

433

434 **Anthelmintic resistance in sheep**

435 Eight of the studies reported on the resistance of nematodes to anthelmintics, either
 436 generally, or specifically for *Teladorsagia* and *Trichostrongylus* (Table 13). In their study of
 437 122 sheep farms in Wales, Mitchell et al., (2010) reported nematodes resistance in 100
 438 farms (82.0%) consisting of resistance to benzimidazole only, benzimidazole and levamisole,
 439 and to levamisole only, in 56 (46%), 38 (31%), and six (5%), of farms respectively. In another
 440 study of 58 sheep farms in Wales, Thomas (2015) reported nematode resistance in 47 farms
 441 (81%), consisting of resistance to benzimidazoles, levamisole, and macrocyclic lactones in 44
 442 (75.9%), 32 (55.2%), and 33 (56.9%) of farms respectively. Ten farms had single resistance,
 443 16 farms had double resistance, 13 had triple resistance; and 7 had triple resistance plus
 444 moxidectin (ibid). In a study of 25 sheep farms in England, Glover et al., (2017) reported
 445 resistance for benzimidazoles, levamisole, and macrocyclic lactones in 24 (96%), 15 (60%),
 446 and 18 (67%) of farms. Three farms had single resistance (to benzimidazoles), 11 farms had
 447 double resistance, and ten had triple resistance (ibid).

448

449 Table 13. Nematode resistance

450

Study	No of farms	Nematode	Overall	1-BZ	2-LV	3-ML
Taylor et al., 2009	40	<i>Teladorsagia</i>		97.5%	40%	
		<i>Trichostrongylus</i>		44%	50%	
Mitchell et al., 2010	122	Unspecified	82%	77%	37%	
Burgess et al., 2012	118	<i>Trichostrongylus</i>	18%	17.8%	3.4%	
Jones et al., 2012	11	<i>Trichostrongylus</i>				55%
Stubblings and SCOPS, 2012	16	<i>Trichostrongylus</i>				62.5%
Thomas, 2015	58	Unspecified	81%	75.9%	55.2%	56.9%
Glover et al., 2017	25	Unspecified	96%	96%	60%	67%
Learmount et al., 2016a	14	<i>Teladorsagia</i>		100%		
		<i>Trichostrongylus</i>		100%		

1-BZ = group 1 (Benzimidazole), 2-LV = group 2 (Levamisole), 3-ML = group 3 (macrocyclic lactone)

451

452 Two studies reported on the resistance of *Fasciola hepatica* (liver fluke) in sheep to
 453 triclabendazole. In a study of 26 farms in England and Wales, Kamaludeen et al., (2019)
 454 reported that 21 of the farms (80.8%) showed a reduction in triclabendazole efficacy with
 455 nine farms showing a complete lack of efficacy and no change in post treatment faecal egg
 456 count. Daniel et al., (2012) reported that of 15 farms in the study, seven (six in Wales and

457 one in Scotland) were found to have triclabendazole resistance, though there was no
458 indication of resistance in the ten farms sampled from England.

459

460 **Anthelmintic resistance in cattle**

461 Two studies reported on the resistance to macrocyclic lactones (ivermectin and moxidectin)
462 to *Cooperia oncophora* and *Ostertagia ostertagi* though both studies contained a small
463 number of farms. McArthur et al., (2011) reported that three out of four farms had FECRT
464 results consistent with *Cooperia* resistance to ivermectin. Geurden et al., (2015) reported
465 that out of ten farms, one and five farms had confirmed and inconclusive resistance to
466 moxidectin respectively, and three and four farms had confirmed and inconclusive
467 resistance to ivermectin respectively; resistant species were *Cooperia* and *Ostertagia*.

468

469 *Anti-ectoparasitic usage & resistance*

470 Two articles contained data concerning ectoparasites, one on the usage and one on the
471 resistance of anti-ectoparasitics. Crilly et al., (2015), reported that 61% of farms (39% using
472 injectable macrocyclic lactones and 21 using organophosphate dips) in Scotland use whole
473 flock treatment for *Psoroptes ovis* (sheep scab), and Doherty et al., (2018), reported on the
474 novel resistance of *Psoroptes ovis* to macrocyclic lactones in a study of four farms in England
475 and Wales.

476

477 **Discussion**

478 **General**

479 Although the importance of anti-infectives and the risk of resistance development are
480 widely discussed (DANMAP 2016, Dorado-Garcia *et al.* 2016, Veldman et al., 2017), we
481 identified a low number of publications (40 papers and two report series) reporting use or
482 resistance in sheep and cattle in Britain. There were marked differences between the
483 number of papers focussing on cattle compared to sheep, with 60% of the papers focusing
484 on usage and 76% on resistance in cattle only. Similarly, both report series only contained
485 primary antimicrobial usage data in cattle and not in sheep. Cattle, especially dairy, may be

486 the greater focus of attention due to the more intensive way they are farmed, with
487 increased contact time between professionals (both farmers and veterinarians) compared to
488 sheep. Other ways that cattle gain more attention than sheep is that beef markets are
489 offered more protections under the EU's Common Market Organisation than sheep markets
490 and additionally, beef is consumed, exported and imported more than sheep meat (AHDB
491 2019a, 2019b). This gap in interest and knowledge of what appears to be a neglected
492 species warrants more attention and research.

493 Antibiotic usage

494 From the data extracted in this review, antibiotic use in sheep and cattle in Britain appear
495 similar to each other, similar to the level observed in poultry, and below the UK average for
496 all livestock (which is elevated by the relatively high usage levels reported in pigs). The
497 marked difference to pig production is likely due to the less intensive nature of production
498 compared to the pig sector, where prophylactic and metaphylactic use of antibiotics to
499 avoid infectious diseases occurs in many farrow-to-finish and fattening farms (Lekagul *et al.*
500 2019). While poultry production in the Britain is often highly intensive, the ability to achieve
501 high levels of biosecurity (such as occurs in closed housing systems) support production
502 systems that are not heavily reliant on antibiotics (DEFRA 2020). However, a major caveat of
503 these findings is the poor level of coverage afforded to sheep and cattle (especially beef
504 production systems) in Britain; small sampling sizes with frequent use of convenience
505 sampling over random sampling are likely to lead to unrepresentative results. In
506 comparison, the pig sector utilises an electronic medicine book (eMB-pigs) to allow farmers
507 to regularly upload antibiotic usage and represents 87% of UK pig producers (DHSC 2019).
508 Mastitis being the most common use for antibiotics in dairy cattle in Britain is consistent
509 with other high dairy producing countries such as the USA and New Zealand (Denis *et al.*
510 2009; Landers *et al.* 2012). Antibiotic usage in dairy cattle due to mastitis has followed a
511 downward trend over the last three years showing reductions in both total usage and in dry
512 and lactating cow treatments. As with other livestock production systems in the UK,
513 tetracyclines and beta-lactam antibiotics (penicillins and first generation cephalosporins)
514 were commonly used antibiotics in sheep and cattle (VMD 2019b), and reflects the WHO's
515 position on restricting the use certain antibiotics (such as third and fourth generation
516 cephalosporins and fluoroquinolones) in non-human species (WHO 2019). Globally,

517 tetracyclines remain the most commonly used antibiotics in livestock production, and are
518 one of the antibiotic groups used for growth promotion in countries which have yet to ban
519 this practice (Granados-Chinchilla and Rodríguez 2017).

520 Many of the scholarly articles described antibiotic usage using in a proportional metric
521 focused at the farm level. While these types of metrics are potentially useful for comparing
522 temporal and spatial trends and providing relatively easy ways of measuring use before and
523 after an intervention, they remain specific to a species, disease, or practice, and are not
524 readily comparable outside of their own sector. However, in this review there were limited
525 instances of proportional metrics being used to make serial or temporal comparisons, thus
526 limiting their usefulness. Furthermore, as the proportional metrics are set at the farm level,
527 they may inflate the magnitude of usage compared to metrics set at the level of individual
528 animals. The production of quantifiable metrics, such as mg/PCU or mg/kg, provide a
529 standardised approach allowing comparisons of usage between species, sectors (livestock
530 and human), and countries, and are advocated as harmonised indicators by both the
531 European Centre for Disease Prevention and Control and the UK One Health report on
532 antibiotic use (VMD 2019a). However, metrics such as mg/kg do not account for the
533 variation in dosage of different antibiotics; for example, newer generation drugs may have a
534 lower mg/kg dose than older ones; thus limiting the use of new generation drugs in favour
535 of older ones may lead to a higher overall mg/kg despite effective antibiotic stewardship
536 (Mills *et al.* 2018). To compensate for this, metrics such as the defined daily dose can be
537 utilised, where the total mg of medicine used is divided by the daily dose, but add an
538 additional level of complexity to data generation. Quantifiable metrics can either be
539 generated from a 'top down' (or consumption level) approach, using national sales data and
540 estimations of total livestock populations (as in the VMD or RUMA reports) and so remain
541 aggregated at the species level; or from a 'bottom up' approach, using veterinary practice
542 sales and farm holding data (as used by Davies *et al.* (2017) and Hyde *et al.* (2017)), and so
543 be more complex and time consuming to generate than consumption level data.
544 Consumption level data can also face problems when antibiotics are licenced for use in
545 more than one species and assumptions need to be made on how usage is divided across
546 species. Given the requirement of farm assurance schemes for farmers to keep records of
547 antibiotic usage, and the high level of digitalisation of veterinary practice sales data,

548 generating additional 'bottom up' quantifiable metrics with a wider coverage than is
549 currently available should be possible, albeit not necessarily feasible; Jones-Diette *et al.*
550 (2016) state that veterinary research using electronic records is hindered by the multitude
551 of practice management systems used in the UK.

552 Antibiotic resistance

553 Although resistance to some antimicrobials (using *E.coli* as a marker) appears to have
554 decreased in sheep and cattle in England and Wales over the last few years, levels of
555 resistance remain high, particularly for tetracyclines, penicillins, aminoglycosides and
556 sulphonamides in both species and there is some evidence of increasing levels of resistance
557 in Scotland. Additionally, many of the sheep and cattle pathogens responsible for
558 economically important issues such as mastitis and respiratory diseases have high levels of
559 resistance to tetracyclines, one of the most commonly used antibiotics. However, as these
560 findings are derived from bacterial samples submitted to veterinary laboratories selection
561 bias should be considered. Given that submitting samples for bacterial culture and
562 sensitivity is not routine practice for all cases of mastitis or respiratory disease the data will
563 likely reflect the more troublesome clinical cases which have not responded to first line
564 treatment, and so resistance levels in the general population may be lower than reported
565 here. With the exception of ampicillin and neomycin in cattle, resistance of pathogens to
566 other major groups of antibiotics remains low for both species, providing, at least for now,
567 effective alternative treatment options.

568 From a One Health perspective, monitoring the levels of antibiotic resistance in zoonotic
569 pathogens in animals forms an important part of national action plans to tackle
570 antimicrobial resistance. The high level of antibiotic resistance observed in *E. coli* in both
571 sheep and cattle is concerning given that ruminants are an important reservoir for zoonotic
572 verotoxigenic *E. coli* (Fairbrother and Nadeau 2006). While it may appear encouraging to
573 observe that resistance in *E. coli* to enrofloxacin remains below 10% for both sheep and
574 cattle across Britain, fluoroquinolones remain an important group of antibiotics in the
575 treatment of *E. coli* in humans, with increasing reports of resistance in people with uro-
576 genital infections (Zaytoun *et al.* 2011; Talan *et al.* 2016). As with *E. coli*, livestock play an
577 important role in the zoonotic transmission of *Salmonella*, a major cause of human food
578 poisoning. The lower rate of antibiotic resistance seen in *Salmonella* in sheep and cattle

579 compared to *E. coli* is reflected in findings from other ruminant populations (Scott *et al.*
580 2012). These lower rates of antibiotic resistance may be explained by the less ubiquitous
581 nature of *Salmonella* in ruminant intestinal tracts than *E. coli* (Fegan *et al.* 2004; RODRIGUEZ
582 *et al.* 2006) leading to a lower antibiotic resistance selection pressure for *Salmonella*.

583 Anthelmintics

584 Sheep gained more attention than cattle in the area of anthelmintic usage and resistance
585 which may be due to some of the inherent differences between these two species. Sheep
586 experience an increase in faecal parasite output around lambing related to a relaxation of
587 immunity at this time, thought to be more profound in the presence of twins (or triplets), a
588 common occurrence in this species (Fthenakis *et al.* 2015). There is a perception that cattle
589 suffer less with worm burdens than sheep (with the industry led COWS advising that adult
590 cows do not need monitoring for worms unless a problem occurs (COWS 2019a)) and our
591 finding that more data exists for sheep than cattle is reflected in global trends on
592 anthelmintic research (Sutherland and Leathwick 2011).

593 Anthelmintic usage

594 The small number and fragmented nature of studies identified by this review describing
595 anthelmintic usage, and the lack of available national sales data, prevented the
596 identification of trends in either sheep or cattle. Collecting data on anthelmintic usage may
597 be confounded by the fact that they are prescribed at a farm rather than animal level, but it
598 should still be possible to see serial and temporal trends. Given the negative economic
599 burden of parasites on livestock production (gastrointestinal parasites are estimated to cost
600 the British sheep industry £84 million annually (Nieuwhof and Bishop 2005)) and two major
601 industry led initiatives to control anthelmintic usage (SCOPS and COWS), this lack of data is
602 surprising, and warrants addressing. For example, it would be prudent to investigate
603 whether the difference identified by Learmount *et al.* (2016) in their small number of SCOPS
604 and non-SCOPS farms, exists on a wider scale, and thus be able to validate the benefit for
605 farmers to follow such guidelines.

606 Anthelmintic resistance

607 The high levels of resistance of nematodes in British sheep and cattle to group 1-3
608 anthelmintics is reflected by global trends in livestock (Mphahlele *et al.* 2019). This finding is

609 concerning, especially given the small number of group 4 and 5 anthelmintics currently
610 available. However, as with anthelmintic usage, the small number of studies focusing on
611 anthelmintic resistance identified by this review warrants attention. The SCOPS guidelines
612 recommend that sheep farmers perform faecal egg counts every two to four weeks during
613 the grazing seasons, and so it could be assumed that data exists at the farm or veterinary
614 practice level detailing anthelmintic resistance on a wider scale than is currently reported.

615

616 Conclusion

617 From the findings of this review we recommend that additional data is needed to
618 understand the current usage of antimicrobials in sheep, and the current usage of, and
619 resistance to anthelmintics in sheep and cattle in Britain. Given the national importance of
620 sheep farming, the lack of research afforded to this species identified by this review is
621 concerning. As identified by two articles in this review, veterinary practice sales data
622 provide a potential valuable resource for measuring antimicrobial usage if effective methods
623 of collecting and collating data can be accomplished on a national scale. When collating and
624 reporting data on antimicrobial usage, researchers and governing bodies should take efforts
625 to produce metrics which are comparable across species, sectors, and time; some of the
626 findings identified by this review were limited in their usefulness due to a lack of
627 comparability. Currently, data on antibiotic resistance in sheep and cattle in Britain is
628 subject to selection bias, being based on specimens from clinical cases, an issue which could
629 be addressed through the development of an active surveillance system, though such a
630 system would require access to adequate resources on a national scale. Additionally, efforts
631 could be made to access data on anthelmintic resistance which exists as part of individual
632 farm health plans so that an assessment can be made about the effectiveness of current
633 strategies to control the development of resistance.

634

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