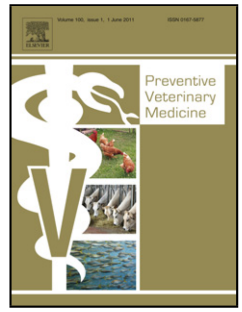

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Antimicrobial & antiparasitic use and resistance in British sheep and cattle: a systematic review

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Abstract

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

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

Antibiotic usage in sheep and cattle in Britain appear to be below the UK average for all livestock and tetracyclines and beta-lactam antibiotics were found to be the most commonly used. However, the poor level of coverage afforded to these species compared to other livestock reduced the certainty of these findings. Although resistance to some antibiotics (using *Escherichia coli* as a marker) appeared to have decreased in sheep and cattle in England and Wales over a five-year period (2013-2018), levels of resistance remain high to commonly used antibiotics. The small number and fragmented nature of studies identified by this review describing anthelmintic usage, and the lack of available national sales data, prevented the identification of trends in either sheep or cattle.

We recommend that additional efforts are taken to collect farm or veterinary level data and argue that extraction of this data is imperative to the development of antimicrobial and antiparasitic resistance strategies in Britain, both of which are needed to reduce usage of these anti-infective agents, curb the development of resistance, and safeguard national agricultural production. Additionally, metrics produced by this data should be generated in a way to allow for maximum comparability across species, sectors, and countries.

Key words: Antimicrobial, antibiotic, antiparasitic, cattle, beef, sheep, Britain

Introduction

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

While the interactions between human, animal, and environmental microbiomes are complex and not fully understood, evidence exists linking the use of antibiotics in one microbiome to the prevalence of resistant organisms in another. Occupational exposure to livestock has been reported as a risk for human health, particularly among veterinarians, farmers, livestock cullers, and slaughterhouse workers, who are exposed to organisms such as livestock associated methicillin resistant *Staphylococcus aureus* (MRSA) and *Coxiella burnetii* (Klous et al., 2016; Rossi et al., 2017; Tang et al., 2017). While reducing the use of antimicrobials in one population is known to be correlated with a reduction in resistance in the same population, evidence linking reductions of use in livestock with reductions of resistant organisms in humans is currently scarce (Bennani et al., 2020; Dorado-García et al., 2016; Tang et al., 2017; Træholt Franck et al., 2017; Veldman et al., 2017). Thus, while measures to reduce antimicrobial usage in farming provide safeguarding mechanisms to protect their therapeutic use in livestock, delineating the benefit such measures have to protect the therapeutic use of antimicrobials in humans remains challenging.

Although there are calls to govern the use of antimicrobials at an international level (Padiyara et al., 2018; Woolhouse et al., 2015), with guidance documents and action plans from global bodies such as the World Health Organisation (WHO), Food and Agriculture Organisation (FAO), and the World Organisation for Animal Health (OIE), (FAO, 2016; OIE, 2016;

WHO, 2019), there is no legally binding international treaty, no Montreal or Kyoto protocol, on how they should be used or documented (Heymann and Ross, 2019). At a national level, there are various best practice guidelines available to antimicrobial and antiparasitic users in livestock in Britain, such as the UK government's One Health report on antibiotic use and resistance (VMD, 2019) and five-year action plan for antimicrobial resistance (DHSC, 2019), the British Veterinary Association's policy statement on the responsible use of antimicrobials in food producing animals (BVA 2019), and the industry led initiatives Sustainable Control of Parasites in Sheep (SCOPS, 2019) and Control of Worms Sustainably (COWS, 2019a). To date, the use of antimicrobials in livestock in Britain is governed by EU (indirectly) and national legislation, which include the 2006 ban on antibiotics being used as growth promoters and a 2018 proposal to restrict the routine use of prophylactic and metaphylactic antibiotics (due to come into effect in 2022) (European Parliament, 2019). Although possible to repeal EU legislation post-Brexit, it is likely the UK will adopt this legislation after its exit as the UK has been one of the forerunners of effective voluntary strategies to reduce antimicrobial use driven by strong private-public partnerships and private industry involvement and leadership.

In Britain, the Veterinary Medicines Directorate (VMD; an agency of the Department of Environment Farming and Rural Affairs) regulates medicine registration and use. The National Office of Animal Health (NOAH) and the Responsible Use of Medicines in Agriculture Alliance (RUMA), two industry initiatives, set the background of what antimicrobials are available and how they are used in livestock. And yet, apart from pigs and poultry, the level of use of antimicrobials in British livestock production is relatively unknown at farm level. Often, due to multi-species registration of medicines, amounts of antimicrobials are stated at livestock level and not species or farm level. Although farmers are legally required to record the amount of antimicrobials they have used (DEFRA, 2019), this data is used for individual farm management and farm assurance schemes, and not stored in a central database and therefore not readily available for antimicrobial usage surveillance.

Usage of antibiotics is calculated through national sales data submitted by pharmaceutical companies to the VMD in accordance with the Veterinary Medicines Regulations 2013. While this inferred usage has good coverage for some livestock species (for example usage in salmon farming is 100% complete), there is only 30% coverage for dairy cattle, 5.5% coverage for beef cattle, and no known sales data coverage for sheep (UK-VARSS, 2019). Additionally, as antimicrobials are often registered to multiple livestock species, sales cannot be reliably related to a certain species, unless the drug of use is solely registered to said species (for example products solely licensed to fish). Antibiotic usage data are collected and submitted voluntarily by different livestock stakeholders to the VMD. This was the result of a collaboration between RUMA and the VMD and first published in 2014 (UK-VARSS, 2014) with only usage data from the poultry sector until more data became available in the subsequent years. Additionally, although the UK participates in mandatory EU-wide antibiotic resistance monitoring, in 2018 samples were only taken from poultry (UK-VARSS, 2019) and so understanding the links between antimicrobial usage and resistance at the animal and farm level is challenging.

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

Methods

Search strategy

A systematic literature review was conducted in line with PRISMA guidelines (Moher et al., 2015). First, an *a priori* protocol was produced which set out the primary and secondary objectives and the review question; namely to (1) identify and describe the existing literature detailing the level of usage and resistance to antimicrobials and antiparasitics in British[1] sheep and cattle production systems, and (2) identify any research gaps within this topic. Goats were not included in this review due to their relatively small contribution to British agriculture; there being approximately 100,000 goats in Britain compared to 10 million cattle and 34 million sheep (Anzuino et al, 2019; DEFRA, 2020b). Inclusion criteria were defined based on the *population*, *intervention*, *comparison*, *outcomes* of an article, and *study* design framework (PICOS, adapted from Chatterjee *et al*., (2018)) and included; English language, peer-reviewed texts and reports, which had a focus on sheep and/or cattle raised for meat production in Britain (England, Wales, and Scotland) published in the last ten years; further details are given in Supp. 1 (section 6). The search was conducted on the 11th and 12th June 2019 in Scopus, Web of Science and Medline databases. These three databases were selected to provide a high level of article recall across biomedical articles (Bramer et al., 2017).

Search terms were derived using the Boolean operator OR for the following four themes, (1) anti-infective agent, (2) livestock population[2], (3) location, and (4) focus, before being

[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.

combined using the Boolean operators ‘AND’ and ‘AND NOT’ (Table 1). The term ‘UK or United Kingdom’ was included at this stage to screen for any articles which may contain information on England, Scotland, or Wales.

To complement the search in scientific databases and achieve a complete systematic review, grey literature was searched using the methodology described by Mahood *et al.* (2014) to screen for data sets and reports. Rather than using open search engines (e.g. Google.com) which may result in unreliable sources, we targeted government data sets (Piasecki et al., 2018). The UK’s government’s data repositories[3] were searched using the same search terms and parameters as described in Table 1. The only difference is that the government search function is not as sophisticated; only using the Boolean operator ‘AND’.

Relevance screening and full text appraisal

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

[3] https://www.gov.uk/search/research-and-statistics

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

Data extraction

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

Results

Summary of articles

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

Descriptive statistics of selected articles and reports

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

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

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

Antibiotic use

Antibiotic usage was detailed in the results of nine (23%) of the articles (five focused on cattle and four focused on sheep) (Supp. 3; Table 1). Seven of the nine articles (78%) targeted farmers for data collection using a questionnaire-based approach and in the remaining two veterinary sales data were used.

The five reports used antibiotic sales data collected from veterinary practices and pharmaceutical companies as part of nationwide antibiotic use surveillance. For cattle, data on antibiotic usage were reported by RUMA and the UK-VARSS over a four- and five-year period, respectively. The RUMA reports use benchmark values for antibiotic usage in dairy cattle provided by two groups of dairy farms from Kite Consulting and Solway Vets (n=674) and from Kingshay consultants (n=409). The 2019 RUMA report contained information on 3,458 beef farms (representing 5.5% of British production) and 2,978 dairy farms (30% of the national herd) collected from veterinary practice sales data by FarmVet Systems[4]. For sheep, the reports contained information on antibiotic usage from a single study by Davies *et al.* (2017) already included in this review.

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

Antibiotic usage in sheep

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

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

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

Antibiotic usage in cattle

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

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

The UK-VARSS and RUMA reports contained antibiotic consumption data from 2013-2018 for dairy and beef production systems and are shown in tables 3 and 4.

Antibiotic resistance

Of the 40 articles, 16 contained information about antibiotic resistance; 12 (75%) about resistance in cattle, three (19%) in sheep and one of the studies contained information about both cattle and sheep (6%) (Supp. 3; Table 2).

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

The 2018 UK-VARSS report contained information on antibiotic resistance in both sheep and cattle (as well as other animals) collated from samples sent to the Animal and Plant Health Agency (APHA) laboratories for diagnostic purposes (UK-VARSS, 2019). Antibiotic resistance was reported for the major livestock bacterial pathogens (such as species causing mastitis and respiratory disease) as well as marker bacterial species significant to human health (such as *E. coli* and *Salmonella* species) collected from livestock faecal samples (Supp. 3; Table 3).

Antibiotic resistance in sheep

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

The most recent UK-VARSS report showed high a level of resistance to tetracyclines in *S. dysgalactiae* and *Mannheimia haemolytica* (Table 5; UK-VARSS, 2019).

High levels of antibiotic resistance were reported in isolates of *E. coli* from sheep in England, Wales, and Scotland, with the highest levels detected to tetracycline, ampicillin, and spectinomycin in all countries, streptomycin in England and Wales, and amoxicillin/clavulanate in Scotland (Figure 2; UK-VARSS 2013, 2015, 2019). Levels of resistance were found to be decreasing in *E. coli* in sheep in England and Wales, while levels of resistance in sheep in Scotland showed an increase over the last two years.

In 2018, the highest level of resistance in *Salmonella* species from sheep in England and Wales was to streptomycin (7.6% of isolates), and in Scotland was to sulphonamide compounds (11.8% of isolates) (Figure 3; UK-VARSS 2013, 2015, 2019).

Antibiotic resistance in cattle

Four studies reported on the resistance profiles of *S. aureus;* two examining isolates from mastitis cases and two examining isolates from bulk milk samples. Thomas et al., (2015) found that of the 38 *S. aureus* isolates from mastitis cases, 31.6% were resistant to penicillin G, and García-Álvarez et al., (2011) found that of the 940 *S. aureus* isolates from mastitis cases, 2.6% were resistant to methicillin, though none were positive for the *mecA* gene (used to confirm methicillin-resistant *S. aureus* [MRSA]). Paterson et al. (2012) identified 300 MRSA isolates from 1500 bulk milk samples and found that seven of the isolates (originating from five geographically remote locations) were *mecA* positive and belonged to the clonal complex CC398. Another study from the same author documented the presence of *mecC* MRSA in ten out of 375 (2.7%) English farms and one sample of *mecA* MRSA (Paterson et al., 2014).

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

Studies which investigated *Enterobacteriaceae* species included those which looked for extended spectrum beta lactamase (ESBL) markers in various bacteria and those which reported on resistance in specific bacterial species (Table 6).

Cheney et al. (2015), found high levels of resistance in *E. coli* to sulphonamides (73.6% of isolates), tetracycline (70.7% of isolates), ampicillin (69.5% of isolates), and streptomycin (48.5% of isolates). The most recent UK-VARSS report recorded a high level of resistance to tetracyclines in the following bacterial species: *S. dysgalactiae, Pasteurella multocida, S. uberis*, and *Mannheimia haemolytica* and a high level of resistance to neomycin in *S. uberis* (Table 7; UK-VARSS, 2019)

Across Britain the highest levels of resistance in *E. coli* from cattle were recorded to ampicillin and tetracycline, with the level of resistance being particularly high in England and Wales. Resistance levels were found to be decreasing in *E. coli* from cattle in England and Wales. While resistance levels were also found to be decreasing in *E. coli* from cattle in Scotland from 2013 to 2017, resistance increased in 2018 (Figure 4; UK-VARSS 2013, 2015, 2019)

In 2018 the highest level of resistance in *Salmonella* species from cattle in England and Wales was to streptomycin and sulphonamide compounds (both 13.9% of isolates), and in Scotland was to sulphonamide compounds (15.7% of isolates) (Figure 5; UK-VARSS 2013, 2015, 2019).

Anthelmintic use

Of the 40 articles, six (15%) looked at anthelmintic usage; five in sheep and one in cattle (Supp. 3; Table 4). All of the studies used farm level data to measure usage and was either captured by farmers self-reporting through questionnaires (n=5), or by ascertaining baseline usage levels before conducting trials into anthelmintic resistance (n=1). No grey literature were found reporting anthelmintic usage.

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

Anthelmintic use in sheep

Of the six studies, two described the routine use of anthelmintics. In a study of 118 sheep farms, Burgess et al., (2012) reported that 99% of farmers gave treatment against nematodes and in a study of 600 farms, Morgan et al., (2012) reported that 93%, 67%, and 58% of farmers routinely treated against nematodes, liver fluke, and tapeworms respectively. Two studies reported on specific farming practices; in their study of 615 sheep farms, Lima *et al.* (2019) reported that farmers administered a group four or five anthelmintic (monepantel and derquantel) to 32% and 28% of ewes and rams at quarantine. Crilly et al., (2015) reported that 27 out of 38 farmers (71%) used moxidectin (a macrocyclic lactone) for the periparturient treatment of ewes. Macrocyclic lactones (group three anthelmintics) were reported by three studies to be the most commonly used anthelmintic against nematodes; 56% of 118 farms (Burgess et al., 2012), 47% of 600 farms (Morgan et al., 2012), and 84% (SCOPS farms[5]) and 70% (non SCOPS farms) in a study of 14 farms (Learmount et al., 2016). Benzimidazoles (group one anthelmintics) were reported to be used against nematodes in 31% of 118 farms (Burgess et al. 2012), 26% of 600 farms (Morgan et al., 2012), and 7%

[5] SCOPS – Sustainable Control of Parasites in Sheep (SCOPS, 2019)

(SCOPS farms) and 21% (non SCOPS farms) in a study of 14 farms (Learmount et al., 2016). Levamisole (group two anthelmintics) had the lowest reported use, ranging from 28-31% of 118 farms (Burgess et al., 2012), 16% of 600 farms (Morgan et al., 2012), to 9% of 14 farms (Learmount et al., 2016).

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

Anthelmintic usage in cattle

Only one study, (Bellet et al., 2018) consisting of 43 farms reported on the use of anthelmintics in cattle and found that farmers routinely used anthelmintics on 85% and 44% of their young stock and adult cows respectively. As with the sheep studies, the most common anthelmintic class used in young stock was macrocyclic lactones (89% of farms), which is consistent with the industry led cattle parasite guideline Control of Worms Sustainably (COWS) which recommend macrocyclic lactones as a first line treatment against the parasites *Ostertagia ostertagi* and *Cooperia oncophora* (COWS, 2019b).

Anthelmintic resistance

Twelve of the 40 studies (30%) reported on anthelmintic resistance; ten in sheep and two in cattle (Supp. 3; Table 5). No grey literature sources were found reporting anthelmintic resistance.

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

Anthelmintic resistance in sheep

Eight of the studies reported on the resistance of nematodes to anthelmintics, either generally, or specifically for *Teladorsagia* and *Trichostrongylus* (Table 8). In their study of 122 sheep farms in Wales, Mitchell et al., (2010) reported nematodes resistance in 100 farms (82.0%) consisting of resistance to benzimidazole only, benzimidazole and levamisole, and to levamisole only, in 56 (46%), 38 (31%), and six (5%), of farms respectively. In another study of 58 sheep farms in Wales, Thomas (2015) reported nematode resistance in 47 farms (81%), consisting of resistance to benzimidazoles, levamisole, and macrocyclic lactones in 44 (75.9%), 32 (55.2%), and 33 (56.9%) of farms respectively. Ten farms had single resistance, 16 farms had double resistance, 13 had triple resistance; and 7 had triple resistance plus moxidectin (Thomas 2015). In a study of 25 sheep farms in England, Glover et al., (2017) reported resistance for benzimidazoles, levamisole, and macrocyclic lactones in 24 (96%), 15 (60%), and 18 (67%) of farms. Three farms had single resistance (to benzimidazoles), 11 farms had double resistance, and ten had triple resistance (ibid).

Two studies reported on the resistance of *Fasciola hepatica* (liver fluke) in sheep to triclabendazole. In a study of 26 farms in England and Wales, Kamaludeen et al., (2019) reported that 21 of the farms (80.8%) showed a reduction in triclabendazole efficacy with nine farms showing a complete lack of efficacy and no change in post treatment faecal egg count. Daniel et al., (2012) reported that of 15 farms in the study, seven (six in Wales and one in Scotland) were found to have triclabendazole resistance, though there was no indication of resistance in the ten farms sampled from England.

Anthelmintic resistance in cattle

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

Anti-ectoparasitic usage & resistance

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

Discussion

Although the importance of anti-infectives and the risk of resistance development are widely discussed (Træholt et al. 2016, Dorado-Garcia et al. 2016, Veldman et al., 2017), we identified a low number of publications (40 papers and two report series) reporting use or resistance in sheep and cattle in Britain. There were marked differences between the number of papers focussing on cattle compared to sheep, with 60% of the papers focusing on usage and 76% on resistance in cattle only. Similarly, both report series only contained primary antimicrobial usage data in cattle and not in sheep. Cattle, especially dairy, may be the greater focus of attention due to the more intensive way they are farmed, with increased contact time between professionals (both farmers and veterinarians) compared to sheep. Other ways that cattle gain more attention than sheep is that beef markets are offered more protections under the EU's Common Market Organisation than sheep markets and additionally, beef is consumed, exported and imported more than sheep meat (AHDB, 2019a, 2019b). This gap in interest and knowledge of what appears to be a neglected species warrants more attention and research.

Antibiotic usage

From the data extracted in this review, antibiotic use in sheep and cattle in Britain are below the UK average for all livestock (29.5mg/kg; which is elevated by the relatively high usage levels reported in pigs [110mg/kg]), with usage in sheep being similar to poultry (12mg/kg) and approximately half that in cattle (UK-VARSS, 2019). The marked difference to pig production is likely due to the less intensive nature of production compared to the pig sector, where prophylactic and metaphylactic use of antibiotics to avoid infectious diseases occurs in many farrow-to-finish and fattening farms (Lekagul et al., 2019). While poultry production in Britain is often highly intensive, the ability to achieve high levels of biosecurity (such as occurs in closed housing systems) support production systems that are not heavily reliant on antibiotics (DEFRA, 2020a). However, a major caveat of these findings is the poor level of coverage afforded to sheep and cattle (especially beef production systems) in Britain; small sampling sizes with frequent use of convenience sampling over random sampling are likely to lead to unrepresentative results. In comparison, the pig sector utilises an electronic medicine book (eMB-pigs) to allow farmers to regularly upload antibiotic usage and represents 87% of UK pig producers (DHSC, 2019).

Mastitis being the most common use for antibiotics in dairy cattle in Britain is consistent with other high dairy producing countries such as the Netherlands, New Zealand, and the USA (Denis et al., 2009; Kuipers et al, 2016; Landers et al., 2012). Antibiotic usage in dairy cattle due to mastitis has followed a downward trend over the last three years showing reductions in both total usage and in dry and lactating cow treatments. As with other livestock production systems in the UK, tetracyclines and beta-lactam antibiotics (penicillins and first generation cephalosporins) were commonly used antibiotics in sheep and cattle (UK-VARSS, 2019), and reflects the WHO's position on restricting the use certain antibiotics (such as third and fourth generation cephalosporins and fluoroquinolones) in non-human species (WHO, 2019).

Many of the scholarly articles described antibiotic usage using in a proportional metric focused at the farm level. While these types of metrics are potentially useful for comparing temporal and spatial trends and providing relatively easy ways of measuring use before and after an intervention, they remain specific to a species, disease, or practice, and are not readily comparable outside of their own sector. However, in this review there were limited instances of proportional metrics being used to make serial or temporal comparisons, thus limiting their usefulness. Furthermore, as the proportional metrics are set at the farm level, they may inflate the magnitude of usage compared to metrics set at the level of individual animals. The production of quantifiable metrics, such as mg/PCU or mg/kg, provide a standardised approach allowing comparisons of usage between species, sectors (livestock and human), and countries, and are advocated as harmonised indicators by both the European Centre for Disease Prevention and Control and the UK One Health report on antibiotic use (VMD, 2019). However, metrics such as mg/kg do not account for the variation in dosage of different antibiotics; for example, newer generation drugs may have a lower mg/kg dose than older ones; thus limiting the use of new generation drugs in favour of older ones may lead to a higher overall mg/kg despite effective antibiotic stewardship (Mills et al., 2018). To compensate for this, metrics such as the defined daily dose can be utilised, where the total mg of medicine used is divided by the daily dose, but add an additional level of complexity to data generation. Quantifiable metrics can either be generated from a 'top down' (or consumption level) approach, using national sales data and estimations of total livestock populations (as in the UK-VARSS or RUMA reports) and so remain aggregated at the species level; or from a 'bottom up' approach, using veterinary practice sales and farm holding data (as used by Davies *et al.* (2017) and Hyde *et al.* (2017)), and so be more complex and time consuming to generate than consumption level data. Consumption level data can also face problems when antibiotics are licenced for use in more than one species and assumptions need to be made on how usage is divided across species. Given the requirement of farm assurance schemes for farmers to keep records of antibiotic usage, and the high level of digitalisation of veterinary practice sales data, generating additional 'bottom up' quantifiable metrics with a wider coverage than is currently available should be possible, but may be hindered by technological issues; Jones-Diette et al. (2016) state that veterinary research using electronic records is hindered by the multitude of practice management systems used in the UK. Generally, there are few such surveillance systems in European countries, but some examples exist that could provide frameworks for the development of others. In the Netherlands, farmers are required to register details of antibiotic use with the Netherlands Veterinary Medicines Institute which is used to compliment antibiotic sales data in their annual report (SDa, 2019). In Denmark veterinarians are required to report on their usage of antibiotics in all production animals. This data is collated in the VETSTAT database (along with pharmacies and feed mills sales data) and has allowed reporting of antibiotic usage at the herd level since 2001 (AACTING, 2020). In Belgium, since 2017, veterinarians have been obliged to register usage of antibiotics in the Sanitel-Med system, though this requirement currently only applies to pigs, broilers, laying hens, and veal calves (BelVet-SAC, 2019).

Antibiotic resistance

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

From a One Health perspective, monitoring the levels of antibiotic resistance in zoonotic pathogens in animals forms an important part of national action plans to tackle antimicrobial resistance. The high level of antibiotic resistance observed in *E. coli* in both sheep and cattle is concerning given that ruminants are an important reservoir for zoonotic *E. coli* species (Fairbrother and Nadeau, 2006). As with *E. coli*, livestock play an important role in the zoonotic transmission of *Salmonella*, a major cause of human food poisoning. The lower rate of antibiotic resistance seen in *Salmonella* in sheep and cattle compared to *E. coli* is reflected in findings from other ruminant populations (Scott et al., 2012). Combined with the less ubiquitous nature of *Salmonella* in ruminant intestinal tracts than *E. coli* (Fegan et al., 2004; Rodriguez et al., 2006) this suggests that the zoonotic risk of antibiotic resistant *Salmonella* from ruminants could be considered limited.

Anthelmintics

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

Anthelmintic usage

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

Anthelmintic resistance

The high levels of resistance of nematodes in British sheep and cattle to group 1-3 anthelmintics is reflected by global trends in livestock (Mphahlele et al., 2019). This finding is concerning, especially given the small number of group 4 and 5 anthelmintics currently available. However, as with anthelmintic usage, the small number of studies focusing on anthelmintic resistance identified by this review warrants attention. The SCOPS guidelines recommend that sheep farmers perform faecal egg counts every two to four weeks during the grazing seasons, and so it could be assumed that data exists at the farm or veterinary practice level detailing anthelmintic resistance on a wider scale than is currently reported.

Conclusion

From the findings of this review we recommend that additional data is needed to understand the current usage of antimicrobials in sheep and cattle, and the current usage of, and resistance to anthelmintics in sheep and cattle in Britain. Given the national importance of both species, the lack of farm level data collection afforded to these species is concerning. As identified by two articles in this review, veterinary practice sales data provide a valuable resource for measuring antimicrobial usage at the farm level if effective methods of collecting and collating data can be accomplished on a national scale. We argue that extraction of this data is imperative to the development of antimicrobial and antiparasitic resistance strategies in Britain, both of which are needed to reduce usage of these anti-infective agents, curb the development of resistance, and safeguard national agricultural production. When collating and reporting data on antimicrobial usage, researchers and governing bodies should take efforts to produce metrics which are comparable across species, sectors, and time; some of the findings identified by this review were limited in their usefulness due to a lack of comparability. Currently, data on antibiotic resistance in sheep and cattle in Britain is subject to selection bias, being based on specimens from clinical cases, an issue which could be addressed though the development of an active surveillance system, though such a system would require access to adequate resources on a national scale. Additionally, efforts could be made to access data on anthelmintic resistance which exists as part of individual farm health plans so that an assessment can be made about the effectiveness of current strategies to control the development of resistance.

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Declaration of interests:

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

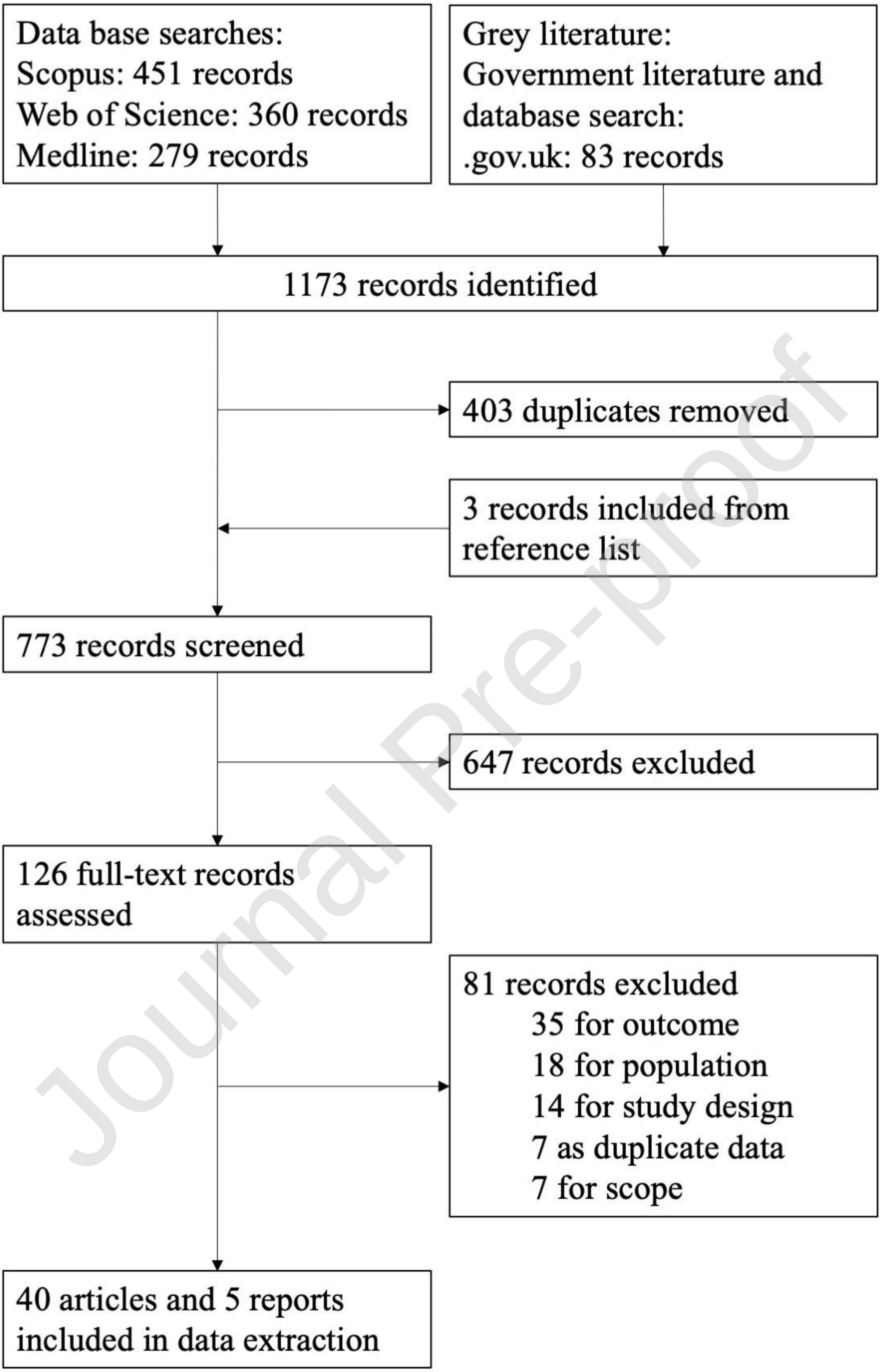
Data base searches:
Scopus: 451 records
Web of Science: 360 records
Medline: 279 records
Grey literature:
Government literature and database search:
.gov.uk: 83 records
1173 records identified
403 duplicates removed
3 records included from reference list
773 records screened
647 records excluded
126 full-text records assessed
81 records excluded
35 for outcome
18 for population
14 for study design
7 as duplicate data
7 for scope
40 articles and 5 reports included in data extraction

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

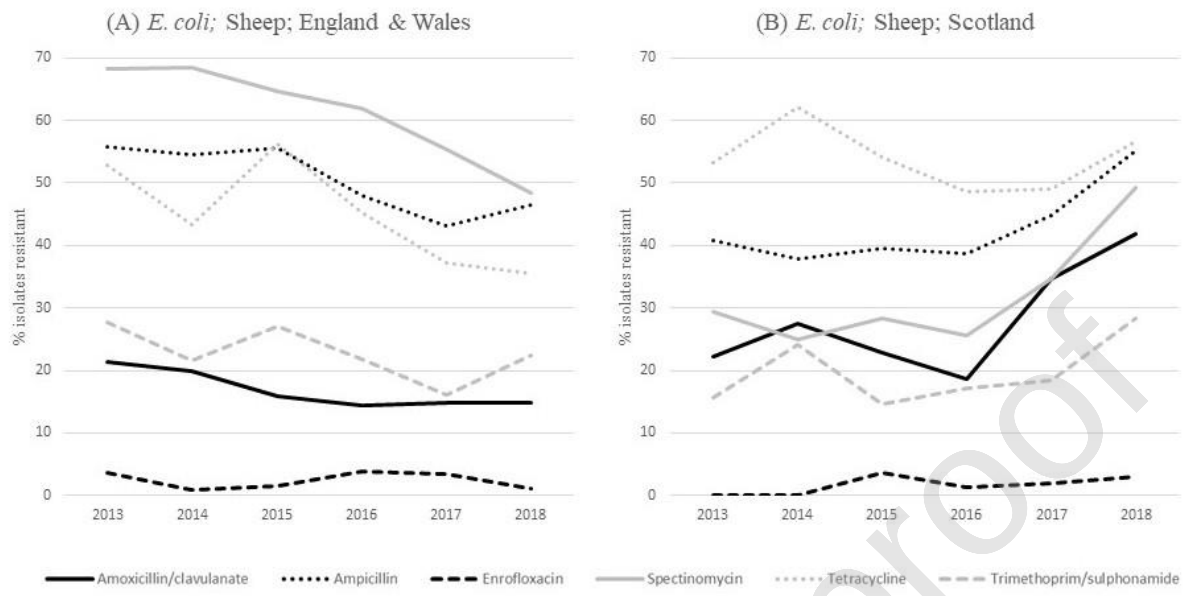

Figure 3. Percentage of *Salmonella* isolates from sheep resistant to different antibiotics in (A) England and Wales, and (B) Scotland

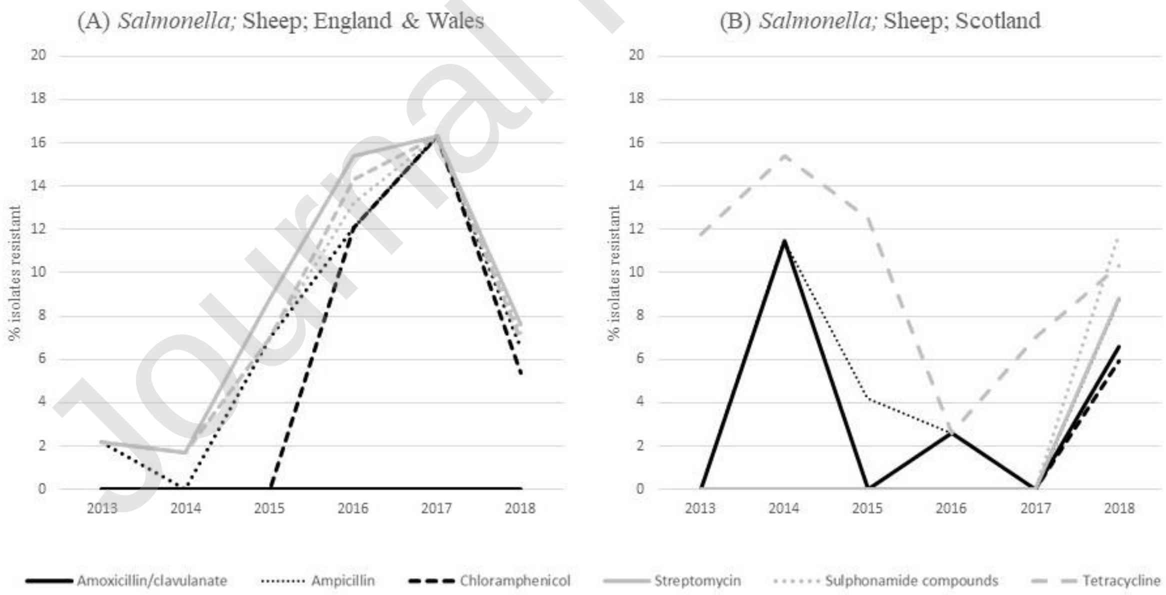

Figure 4. Percentage of *E. coli* isolates from cattle resistant to different antibiotics in (A) England and Wales, and (B) Scotland

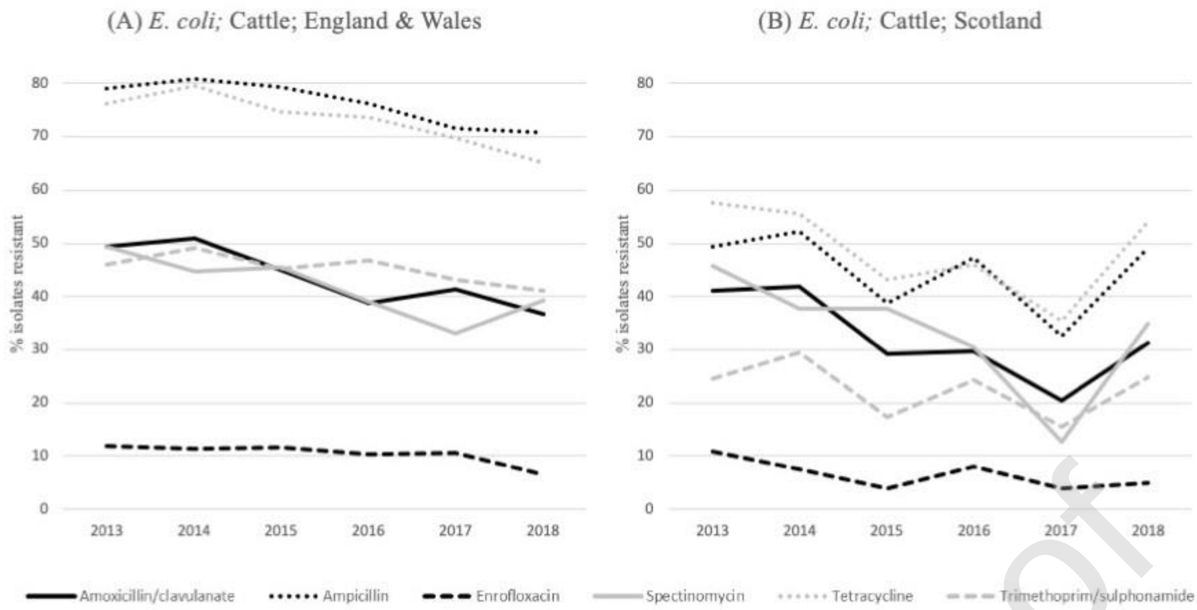

Figure 5. Percentage of *Salmonella* isolates from cattle resistant to different antibiotics in (A) England and Wales, and (B) Scotland

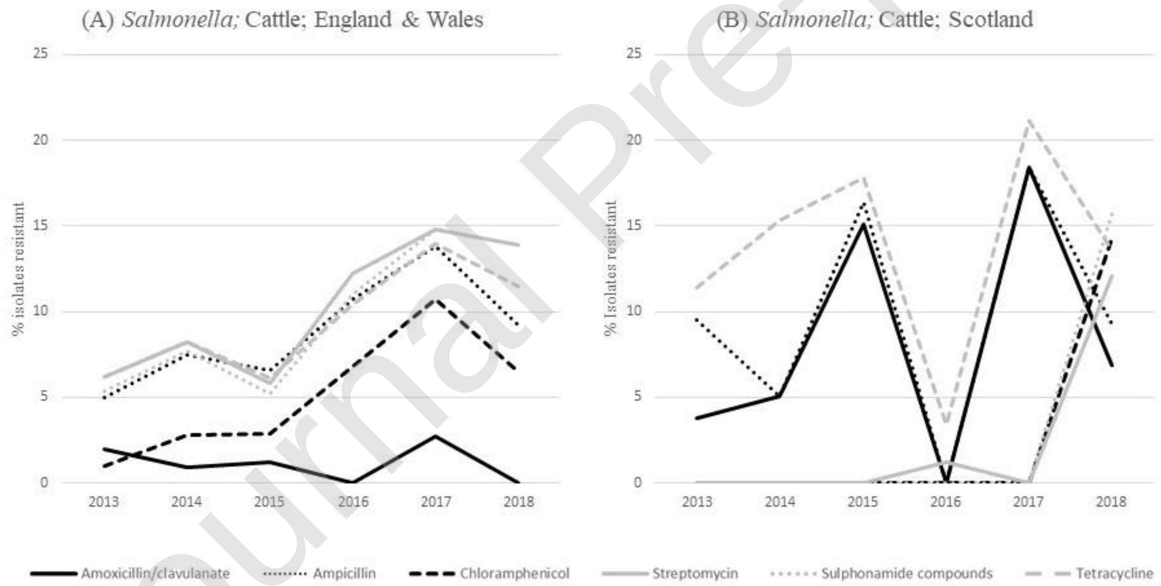

Table 1. Search terms used to build the systematic review

Anti-infective agent	Livestock population	Location	Focus	Exclude
(antimicrobial* OR "anti microbial*" OR antibiotic* OR "anti biotic*" OR 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)	AND (livestock OR cattle OR beef OR cow OR cows OR calf OR calv* OR heifer* OR bull OR bulls OR bovine OR sheep OR lamb* OR ewe OR ewes OR ram OR rams OR ovine OR dairy)	AND (GB OR "Great Britain" OR England OR English OR wales OR welsh OR Scotland OR Scottish OR UK OR "united kingdom")	AND (use OR using OR usage OR resis* OR treatment* OR incidence OR prevalence OR risk OR "risk factor" OR driver)	AND NOT "New south wales"

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

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

Table 3. Antibiotic usage in cattle by class (UK-VARSS, 2019)

Antibiotic	Beef mg/kg (% of total)	% change 2017-2018	Dairy mg/kg (% of total)	% change 2017-2018
Penicillin and 1st 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

Table 4. Antibiotic usage in beef and dairy cattle (RUMA, 2019; UK-VARSS, 2019)

	Baseline (2016)[6]	2017-2018	2018-2019	% change compared to baseline
Total usage (mg/kg)				
FarmVet Systems				
Beef	-	19	21	
Dairy	26.2	16	17	-29.2
Kite consultants & Solway Vets				
Dairy	26.2	23.7	21.9	-16.4
Kingshay consultants				
Dairy	26.2	20.5	17.3	-34.0
Intramammary tubes (DCDVet)				
UK-VARSS				
Dry cow	0.732	0.547	0.644	-12
Lactating cow	0.808	0.694	0.776	-4
Kite consultants & Solway Vets				
Dry cow	0.732	0.5	0.46	-37
Lactating cow	0.808	0.66	0.55	-32
Kingshay consultants				
Dry cow	0.732	0.522	0.519	-29
Lactating cow	0.808	0.801	0.601	-26

Table 5. Antibiotic resistance in major sheep pathogens (UK-VARSS, 2019)

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

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

Table 5. Antibiotic resistance in major sheep pathogens (UK-VARSS, 2019)

Resistant isolates (%)

[6] Baseline data taken from a single source; FarmVet Systems

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

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

Table 6. 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 *E. coli* found on 43.1% of farms
Cheney et al., 2015	Pre-existing lab samples (n=534)	84.1% non-VTEC *E. coli* resistant to at least one antibiotic 56.5% VTEC *E. coli* resistant to at least one antibiotic
Wu et al., 2012	Pre-existing lab samples (n=34)	61.7% of *E. coli* with at least one antibiotic resistant gene
Mueller-Doblies et al., 2018	Pre-existing lab samples (n=244)	69.2% of *Salmonella* isolates resistant to one of more antibiotics
Mellor et al., 2019	Pre-existing lab samples (n=1115)	85.4% of *Salmonella* isolates resistant to one of more antibiotics 74.7% of *Salmonella* isolates resistant to three or more antibiotics

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

Table 7. Antibiotic resistance in major cattle pathogens (UK-VARSS, 2019)

		Resistant isolates (%)						
	Number of isolates	Ampicillin	Amoxicillin/ clavulanate	Enrofloxacin	Trimethoprim	Tetracycline	Neomycin	Tylosin
Common mastitis pathogens:								
Escherichia coli	110	21.8	5.5	2.7	6.4	13.6	2.7	
Streptococcus dysgalactiae	32	0	0			87.5	3.1	0

Streptococcus uberis	84	0	0			34.5	45.2	11.9
Staphylococcus aureus	36	27.8	0			2.8	0	2.8
Common respiratory pathogens:								
Pasteurella multocida	76	2.6	0	0	0	51.3		
Mannheimia haemolytica	44	2.3	0	0	0	50		

Table 8. Nematode resistance

Study	**No of farms**	**Nematode**	**Overall**	**1-BZ**	**2-LV**	**3-ML**
Taylor et al., 2009	40	*Teladorsagia*		97.5%	40%	
		Trichostrongylus		44%	50%	
Mitchell et al., 2010	122	Unspecified	82%	77%	37%	
Burgess et al., 2012	118	*Trichostrongylus*	18%	17.8%	3.4%	
Jones et al., 2012	11	*Trichostrongylus*				55%
Stubbings and SCOPS, 2012	16	*Trichostrongylus*				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., 2016	14	*Teladorsagia*		100%		
		Trichostrongylus		100%		

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