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Review

Global Change and Helminth Infections in Grazing Ruminants in Europe: Impacts, Trends and Sustainable Solutions

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Abstract: Infections with parasitic helminths (nematodes and trematodes) represent a significant economic and welfare burden to the global ruminant livestock industry. The increasing prevalence of anthelmintic resistance means that current control programmes are costly and unsustainable in the long term. Recent changes in the epidemiology, seasonality and geographic distribution of helminth infections have been attributed to climate change. However, other changes in environment (e.g., land use) and in livestock farming, such as intensification and altered management practices, will also have an impact on helminth infections. Sustainable control of helminth infections in a changing world requires detailed knowledge of these interactions. In particular, there is a need to devise new, sustainable strategies for the effective control of ruminant helminthoses in the face of global change. In this paper, we consider the impact of helminth infections in grazing ruminants, taking a European perspective, and identify scientific and applied priorities to mitigate these impacts. These include the development and deployment of efficient, high-throughput diagnostic tests to support targeted intervention, modelling of geographic and seasonal trends in infection, more thorough economic data and analysis of the impact of helminth infections and greater translation and involvement of end-users in devising and disseminating best practices. Complex changes in helminth epidemiology will require innovative solutions. By developing and using new technologies and models, the use of anthelmintics can be optimised to limit the development and spread of drug resistance and to reduce the overall economic impact of helminth infections. This will be essential to the continued productivity and profitability of livestock farming in Europe and its contribution to regional and global food security.

Keywords: helminthoses; ruminants; diagnosis; control; infection risk; global change; climate change; anthelmintic resistance; risk management; spatio-temporal modelling; epidemiology; food security

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1. Impact of Helminth Infection on the Sustainability and Efficiency of Livestock Farming

1.1. Livestock Farming As a Cornerstone of Society

Livestock farming is central to the sustainability of rural communities around the world, as well as being socially, economically and politically highly significant at national and international levels. In the European Union (EU), for instance, there are currently around 88 million cattle, 101 million sheep and 12 million goats [1]. Ongoing socioeconomic and climatic changes will increasingly emphasise the need for food security, obtained from sustainable intensification of agriculture [2]. It is inevitable that the production of meat and dairy products will also have to expand to meet the demands of increasing world population. Efficient ruminant livestock production is crucial to achieving this goal, especially in areas in which land is unsuitable for growing crops [3]. In this context, the competitiveness of livestock farming will largely depend on the degree to which this industry can achieve sustainable optimal production levels under changing environmental and socioeconomic pressures.

1.2. Costs to Economies and Animals

All grazing animals are exposed to helminth infections at pasture and any future intensification of pasture-based systems will likely increase the risk of helminth disease. Gastrointestinal nematodes (GIN) and liver fluke are the two major causes of lost productivity in ruminants, with lungworms also important in some situations. The economic costs of parasitic disease are currently difficult to quantify; however, some estimates exist within the scientific literature. For example, studies in the United Kingdom estimated the cost of parasitic nematodoses of sheep to be on the order of 99 million € per year [4], and in Switzerland, the cost of liver fluke disease has been estimated at 52 million € per year in cattle alone [5]. Within the EU as a whole, annual sales of anthelmintic drugs used to control these infections in ruminants have been estimated to be on the order of 400 million € [6]. It is likely that these figures only represent the tip of the iceberg when it comes to calculating the true cost of livestock helminthoses endemic within the EU [7].

Parasitic gastroenteritis (PGE) in European cattle results principally from infections with *Ostertagia ostertagi* and *Cooperia oncophora* [8]. Although *Cooperia* is less pathogenic than *Ostertagia*, these parasite species usually occur together in the same host, with one contributing significantly to the pathogenic effect of the other. In European sheep and goats, *Teladorsagia circumcincta*, *Haemonchus contortus*, *Trichostrongylus* spp. and *Nematodirus* spp., parasitizing the intestine, are the most pathogenic GIN species, contributing significantly to PGE. Fasciolosis (liver fluke disease), caused by the trematode, *Fasciola hepatica*, is a worldwide infection of livestock, especially sheep and cattle, while lungworms in the genus *Dictyocaulus* cause significant disease in cattle and to a lesser extent in small ruminants. The main effect of all these infections is to reduce production efficiency, although under certain circumstances, mortalities can also be high: up to 20% with genera, such as *Haemonchus*, *Nematodirus* and *Fasciola* [9]. The major economic impact of parasitism is due to sub-clinical infections causing production losses. These costs have become increasingly important in the current economic climate with the low profit margins in the livestock sector.

At present, there is only a limited and fragmented understanding of the true costs of helminth parasitism, including costs associated with its control. This must be rectified if future control strategies are to be economically sensible and well integrated into farming systems. Recent advances in diagnostics, such as quantification of bulk milk anti-nematode antibodies, have enabled improved estimates of the production impacts of parasites in dairy herds and underpin optimized strategies for their control [10–12]. Further gains in understanding are likely to be made by comparing animal production in high and low intervention situations [13] and where anthelmintic efficacy fails. It is only by more fully characterizing and understanding the production impacts of parasites that future control can be optimized effectively.

2. Increased Risks of Helminth Infection in Livestock Due to Global Change

2.1. The Changing Environment

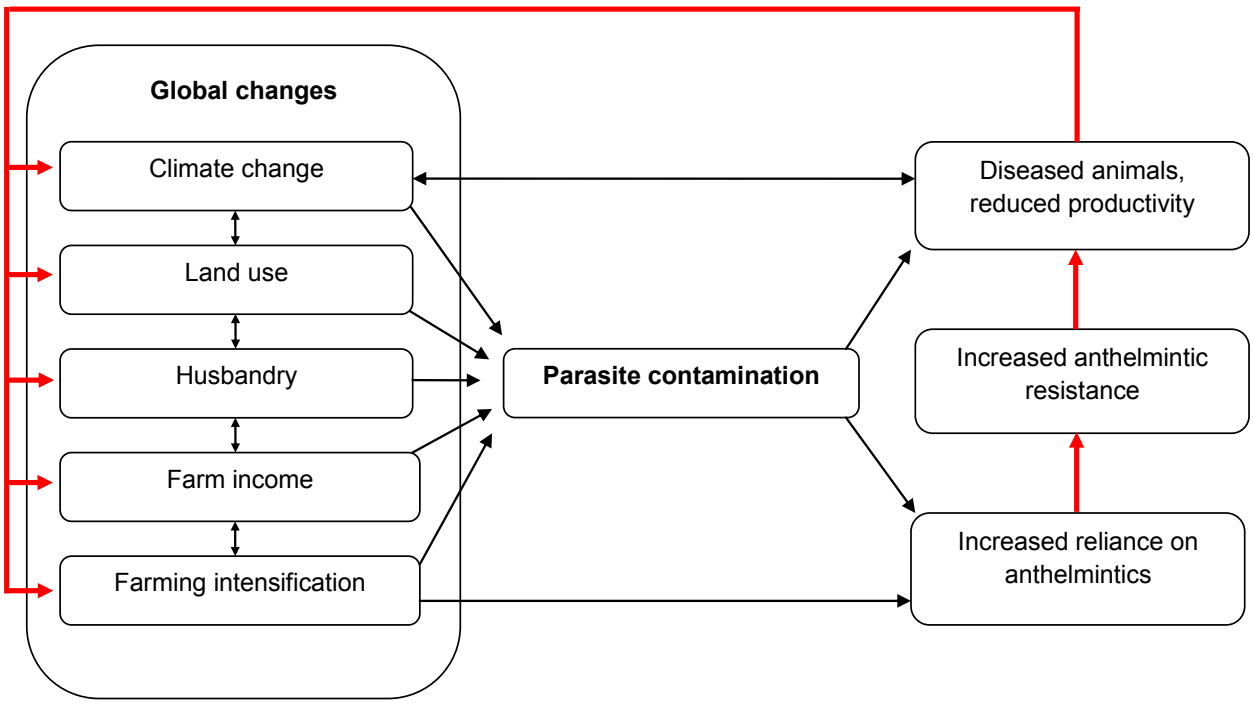
In recent years, sharp increases in helminth-associated disease frequency and intensity have been reported within the ruminant sector in some regions [14]. Climate warming, which in temperate regions tends to increase the developmental success of parasites, might be expected to increase pasture contamination with infective stages and may be one driver behind this trend. For example, there have already been reports of altered seasonal patterns of nematode and liver fluke infections in northern parts of the UK [15,16]. In Switzerland, unpublished data suggest that *H. contortus* transmission is occurring at higher altitudes than previously recorded, and in Sweden, transmission occurs near the Arctic Circle [17]. If these trends continue as predicted, European farmers may be faced with new and unfamiliar parasitological challenges that they are ill equipped to meet. However, the study of the effects of climate change on the endemic diseases of livestock is still in its infancy [18,19], and the effects of additional factors, such as altered land use, the emergence of anthelmintic resistance (AR) and farm management practices, have received little detailed attention [19]. Thus, attempts have been made to integrate the abundant knowledge of environmental, especially climatic, effects on parasite stages outside the livestock hosts into predictive mathematical models, especially focusing on selection for AR [20–24], and some have tried to predict future infection patterns [25]. However, the abundance and distribution of helminth infections of livestock is a complex and dynamic issue affected by a whole range of parameters, including those that could be classed as global changes (Figure 1). The situation is further complicated by interacting regional, seasonal and host-specific factors that influence disease and the fact that helminthoses are usually seen in animals that have concurrent multi-species infections. The fact that global change is much more than climate change alone must be acknowledged and incorporated more fully into future research approaches in this area.

2.2. The Importance of Anthelmintic Resistance

An equally important driver of increased disease and production loss due to helminths is likely to be treatment failure, which is being reported ever more frequently. The increasing occurrence of AR in helminth populations threatens the sustainability, as well as the efficiency of livestock production. Although there are a number of different approaches to the control of helminth parasitism in livestock, including nutritional, immunological and biological interventions [26], at present, effective control

relies almost exclusively on effective anthelmintic drugs. Most of these compounds have broad-spectrum activity, *i.e.*, they kill all the common roundworm species (there are specific products effective against fluke), but effective control ultimately relies on multiple treatments each year. When first introduced, all these drugs were highly efficacious, but frequent and widespread use and misuse has resulted in the emergence of resistant parasite populations, such that AR is now a major global problem, especially (but not exclusively) in parasites of small ruminants [27], and is the greatest threat to the sustainable control of helminthoses in the short to medium term. Anthelmintic inefficacy and resistance has also become apparent in cattle, reported initially in the southern hemisphere [28–30], but more recently also within Europe [31,32].

Figure 1. An association network illustrating how global changes may influence pasture contamination with helminth parasites. Black arrows represent positive enforcement, and those in red (bold) show potential associations arising from global change.



The problem of AR is compounded by the fact that many of these parasite populations are resistant to more than one class of anthelmintic [33,34] and that the prevalence of resistance is increasing inexorably in many regions [35]. Despite the recent introduction of two novel anthelmintic drug classes for sheep [36,37], the situation regarding the development and transmission of AR remains largely unaltered. Accordingly, there is an urgent need to reduce anthelmintic usage, while timing treatments optimally, taking into account global change-driven alterations in parasite seasonality. To maintain or, in some regions, regain control over these parasites, an improved understanding and quantification of the key mechanisms involved in their spatial and temporal prevalence is also paramount.

2.3. The Need for Increased Carbon Efficiency in Ruminant Farming

The increased prevalence of helminths, especially drug-resistant parasites, poses an even more pressing problem against a background of increasing pressure towards lowering the carbon footprint of

ruminant livestock. Worldwide, ruminant livestock farming accounts for 70% of agricultural land use, occupies 30% of the ice-free surface of the planet and produces some 40% of the global agricultural Gross Domestic Product (GDP). Set against this, it is estimated to account for up to 18% of worldwide greenhouse gas emissions [38]. There is a new requirement for European livestock farming to become carbon emission efficiency-driven [39]. Animals emitting greenhouse gasses, while not growing or producing, because of illness, add significantly to a farm's carbon footprint; so, combating infectious and parasitic diseases on livestock farms is essential for any improvements in the carbon efficiency of production [40].

A particular issue regarding AR is that a response to increased infection pressure as a result of climate and other environmental change that relies on increased use of anthelmintic drugs will undermine the sustainability of control, as increased drug use selects more strongly for AR. As drug efficacy declines, production efficiency would be expected to decrease and greenhouse gas emissions per unit production, increase. This could trigger a positive feedback cycle, fuelling ongoing climate change and further increases in infection and its effects.

3. Scientific Priorities to Support Sustainable Helminth Control

The development and implementation of innovative, refined approaches to worm control, targeted at the appropriate regional scale, is a prerequisite for reducing the enormous burden helminth parasitism imposes upon ruminant livestock production. This goal can be supported by exploiting developments in high-throughput technologies coupled to novel diagnostics to identify sub-clinical infections within an affordable and flexible diagnostic capacity. However, the provision of innovative diagnostic tools to identify the species implicated in infections, and individual and/or herd/flock markers of helminthoses, are only the first steps in the process. To have real impact, new diagnostic capacity needs to integrate with decision support tools, such as measures of economic impact [11], predictive disease risk forecasting models and livestock management software. Statistically-based risk models of helminthoses that incorporate Geographical Information System (GIS)-based surveillance, as well as temporally explicit models predicting periods of high risk, could inform farm management responses to regional environmental, climatological, parasitological and socioeconomic changes, and themselves depend on data generated from enhanced diagnostic capacity. In particular, optimising intervention strategies, including extent and intensity of drug use to control worm infections, must be based on evidence. This requires accurate and efficiently collected information on levels of challenge, infection and production loss and integration of this information in such a way that optimal strategies can be devised. Scientific research can support this endeavour in four main fields: (1) diagnosis of helminthoses in livestock at the individual and herd level with specific attention to multi-species infections and the distribution of anthelmintic resistance; (2) prediction of the impact of global changes on the epidemiology of parasitic infections, as well as the distribution and spread of anthelmintic resistance; (3) explanation of current, and future predictions of, seasonal trends in helminth infections of grazing livestock; (4) strategies for the sustainable management of helminth infections in a changing landscape. The rationale for prioritising these areas, and the scientific and technical challenges that they present, are discussed below.

3.1. Diagnosis

Many methods are already available for the diagnosis of helminth infections, clinical and sub-clinical disease and AR, but all have their weaknesses. The principal clinical signs, such as diarrhoea, anorexia and ill-thriftiness are common sequelae of many other infectious diseases and syndromes and, consequently, lack sensitivity and specificity. Many of the methods used to diagnose helminthoses can only be applied to individual animals and/or to hosts infected with one helminth species, with little or no capacity to deal with infections where multiple species are present. Current parasitological, immunological and molecular diagnostic technologies are often labour-intensive and, therefore, expensive, with limited application either on-farm or for large-scale surveillance.

Because helminthoses inevitably involve multiple parasite species, in order to ensure that the appropriate treatment is applied, it is important to identify the key species responsible for the signs of disease and/or production losses. Most routine helminth diagnoses rely on the detection of parasite stages (usually eggs) in faecal samples. Parasitological diagnoses offer the advantage of relatively low cost and can be conducted in non-specialised laboratories; however, the morphological identification of nematode eggs and larvae to the species (or even genus) level is difficult and requires experienced personnel [38]. In some circumstances, for example, treatment decisions based on increasing faecal nematode egg counts in grazing ruminants, specific identification is not a priority. However, control strategies that are truly directed at the major parasitic threats to health and production should be based on more detailed knowledge of these threats, including their economic impact.

Although species specificity is often more easily achievable through immunological detection, a major drawback with these approaches is that they do not necessarily indicate the presence of a currently active infection. A further complication is in obtaining suitable samples, since some tests require invasive procedures, such as blood sampling, which are not routine practices in sheep and cattle. Molecular genetic (Polymerase chain reaction, PCR-based) approaches have potential for this application, because they are sensitive and specific and can be applied to helminth parasite material [41], most notably, eggs and larvae extracted from faecal samples. To date, however, these approaches have tended to concentrate on single species and work best on material derived from single parasites [42,43], which requires considerable upstream processing. Real-time PCR and pyrosequencing approaches have also been developed in an attempt to provide quantitative information on species composition and show much promise, but more development work is required before validated molecular species identification tests can be made available [44,45].

AR is an additional complicating factor with regard to the diagnosis of helminthoses. Currently, the principal means of identifying AR *in vivo* is the faecal egg count reduction test (FECRT), based on a series of pre- and post-treatment individual egg counts. This test has limitations, not only because it is labour intensive, but also regarding the optimum sampling and counting criteria, especially in cattle, and can be confounded by over-dispersed parasite populations [46]. However, the FECRT is still a useful indicator of drug efficacy in the field, since samples can be submitted to diagnostic laboratories by post, but the test does still require simplification and further optimisation to encourage uptake by end-users. There are several *in vitro* bioassays available that examine the effects of differing drug concentrations on parasite behaviour and development, e.g., the egg hatch test (EHT), larval migration inhibition assay (LMIA), larval feeding inhibition assay (LFIA) and larval development test (LDT) [47]. These tests are

useful for characterising single-species parasite isolates in the laboratory, but are not yet sufficiently standardised to be of use as routine diagnostic tests for resistance in the field. Moreover, they do not all work equally well with all available drug classes, e.g., the EHT can only be used to detect benzimidazole (BZ) resistance. Their utility is further compromised by the fact that different parasite species have their own inherent sensitivities to certain drugs, making the interpretation of test results from natural multi-species infections extremely difficult. Since AR has a genetic component, molecular (DNA-based) methods have great potential as putative diagnostic test systems here, too. However, this development requires validated genetic markers for resistance, and to date, this is only available for one drug class (the BZs) and not yet in all species [48]. Nonetheless, sensitive and accurate pyrosequencing assays have been published for the detection of BZ resistance-associated single nucleotide polymorphisms (SNPs) in *Haemonchus* and *Teladorsagia* [49,50] and have shown that BZ resistance allele frequencies correlate well with the outputs from FECRTs conducted in the field [51]. The search for resistance markers for the other drug classes has largely focused on candidate resistance genes, but has not been proven, to date, to be a fruitful exercise [52]. Although whole genome sequencing has the potential to reveal the genetic determinants of resistance, this approach is still very much in its infancy [53].

Cost and speed of reporting remain important barriers to the support of control with accurate diagnosis of helminth infection and disease. The use of emerging high-throughput immunological and molecular-based technologies offers the potential to reduce costs and offer diagnosis at a scale suitable for large-scale monitoring within Europe. The advent of microbead-based technologies has led to the development of a number of multiplex assay platforms, e.g., LUMINEX®, which permit multiple assays to be performed on the same samples and provide a range of versatile assay designs, including antibody/antigen, primer/probe and enzyme/substrate interactions [54–58]. The use of this platform allows the simultaneous determination of several parameters (in theory, up to 100; in practice, probably 10–20) from a single serum sample in a streamlined highly automatable workflow. This greatly enhances test/sample throughput and the efficiency of sample utilisation, both prerequisites for effective surveillance and monitoring activities. Such methodologies are widely used in human diagnostic facilities, but, to date, have not been widely applied in veterinary parasitology. This platform is ideally suited for high-throughput Enzyme-linked immunosorbent assay (ELISA)-based test systems. Possible relevant parameters to be measured include not only circulating parasite antigen or anti-parasite specific antibodies [59–61], but also health indicators, such as markers of inflammation, e.g., acute phase proteins [62], and tissue damage, e.g., pepsinogen [63], for which validated assays already exist.

Multivalent platforms are suited to the incorporation of serological- and molecular-based tests. Prototype multiplex PCR-based molecular assays already exist for the detection of individual GIN species infecting sheep and cattle [43,44]. Such multiplex LUMINEX® assays have already been described for the detection of the protozoan pathogens, *Giardia* and *Cryptosporidium* spp., from faecal samples [64–66], but have not yet been developed or validated for helminth parasites. These high-throughput diagnostic platforms require considerable capital investment and experienced personnel to maintain the instruments and to run assays. There is still a need for relatively simple diagnostic tests that require little specialised equipment and that might, ultimately, have “pen-side” applications. Innovative approaches based on the recently developed loop-mediated isothermal amplification (LAMP) method show promise in this regard. This is a commercially available detection

method to amplify nucleic acids and offers a rapid, accurate and cost-effective diagnosis of infectious diseases [67–70]. LAMP technology has the added advantage that it is not prone to inhibition by contaminants within faecal samples, as is the case with traditional PCR-based methods. These novel analytical platforms also have the potential to detect and quantify anthelmintic resistance-associated DNA polymorphisms in key parasite genera.

3.2. Spatial Epidemiology and Forecasting of Helminth Disease

More efficient targeting of anthelmintic-based control strategies can benefit not only from improved diagnosis, but also prediction of disease threats in space and time. In the ~50 years since the first epidemiologically-based helminth parasite model was published [71], a number of simplified models have been developed for both nematodes and trematodes [72]. However, simplified models often neglect crucial interactions, while those with a more realistic level of detail are usually over-parameterised, making it hard to interpret their output. Most existing models of disease and/or parasite ecology were not constructed against a background of global change and do not, therefore, include crucial factors, such as changing land use and farm management practices. Exclusion of such important drivers leads to a non-realistic output, which might help explain why such models have had a limited impact on parasite control in practice. The climate-based forecasting models previously developed for animal fasciolosis in different areas of Europe, Africa and the USA [73] also require further development to incorporate global change factors, including farm management practices, animal movements and climate change. Therefore, the more realistic models become by incorporating such factors, the less reliably their predictions can be extrapolated to other areas, circumstances and research or control questions. Efforts to model the dynamics and control of helminths in ruminants in other parts of the world [20,23] have value in highlighting general aspects of system dynamics, but ultimately, models for prediction and decision support in Europe should be constructed and validated in relation to local conditions [74]. Models will only be plausible to animal health advisors if shown to work well on the ground, and proper validation is vital if their use in decision support tools is to gain traction. An approach that builds local detail and variation onto a common, general framework for helminth-livestock interactions might, therefore, be a useful way forward.

Ultimately, both spatial and temporal models of parasite occurrence and abundance rely on solid data for their development and validation [75] and can, therefore, benefit from improved high-throughput diagnostics. The prohibitive costs and logistics of conducting extensive and repeated surveys of disease for purely descriptive information on distribution have led to an increased interest in computer-based geospatial technologies. Human and veterinary medicine has seen an increasing reliance on the application of geospatial tools—*i.e.*, GIS, Global Positioning System (GPS), satellite-based remote sensing (RS) and Virtual Globes (e.g., Google Earth^{TM})—to study the spatial and temporal distribution of infectious and parasitic diseases and their vectors [76,77]. Health research based on geospatial tools is considered a timely approach in a changing environment to understand climatic-environmental-health linkages [78]. The application of spatial sampling strategies to animal diseases is relatively new, and the study of pathogen distribution and abundance at a geospatial scale has focused mainly on vector-borne diseases (VBD), mainly due to their direct link with the environment. As an example, 51% of the papers published by the journal, Geospatial Health [79], between 2005 and 2010 dealt with VBD, only 6% with

non-vector transmitted helminths and 19% with trematode infections; however, the latter mainly pertain to schistosomes and, to a lesser extent, *Fasciola*. There therefore seems to be considerable scope for applying existing, as well as new geospatial approaches to understanding and predicting parasite distribution and disease risk in livestock. Important parameters, such as environmental factors and farm management, are also rarely taken into consideration when planning cross-sectional or longitudinal surveys for spatial modelling.

3.3. Predicting the Timing of Parasite Risk

Spatial variation in parasite disease risk enables the design of monitoring and intervention strategies that are locally appropriate, while also providing a systematic basis for assessing trends in risk as a result of global change. However, effective intervention against parasitic disease is temporally sensitive, relying on the coincidence of animal grazing with infective stage availability [80]. The timing of treatment and other actions, including grazing practice and diagnostic monitoring in support of targeted treatment strategies, is therefore very important to the outcome in terms of the reduction of disease challenge and selection for anthelmintic resistance. Moreover, one of the main effects of climate change on parasite epidemiology is likely to be the altered seasonal availability of infective stages [9,81]. For example, warmer temperatures appear to be reducing overwinter survival of GIN of sheep in the UK, but accelerating build-up of infection in summer, leading to decreases in recorded disease in spring, but increases in autumn [82]. Therefore, comprehensive modelling approaches should also consider temporal patterns of infection [83], for example, by building and populating mechanistic representations of the life-cycles of the major helminth species, with components that explicitly incorporate climatic stochasticity, forage availability and utilisation and variation in farm management at the regional level. These can be extended to consider global change scenarios through variation in climate, farm systems and parasite biology, as well as, potentially, parasite adaptation. The extent to which parasite adaptation to changes in climate and management will affect their control has barely been considered in trichostrongyloids beyond drug resistance, with some exceptions [84]. The breadth of this approach and the specific consideration of the spatial scale over which important determinants of epidemiology act are crucial, not only to advancing existing scientific understanding of the processes involved [72], but also to practical application of modelling in support of disease control, in that explicit consideration of the timing of helminth transmission is needed to optimise control strategies. A future vision of mathematical and geospatial modelling for parasite control would combine temporal and spatial aspects, to provide forecasting and scenario analysis tools that are integrated at local, regional and global levels. These could be applied to on-farm decision making through decision support tools, to horizon-scanning for disease threats by industry and animal health authorities and to policy making at national and supra-national levels.

Validation of models with experimental and field data will be crucial to model plausibility. However, model exploration through scenario analysis is also essential to consider the possible effects of global change and, often, is impossible to validate fully, because scenarios will often go beyond the range of past or present experience. For the same reason, purely empirical approaches will be limited in their ability to demonstrate and predict the effects of global change: there is no controlled experiment possible to emulate the scope of global change on parasitism within farming systems as a whole. At the same

time, limited standardisation and centralisation of parasitic disease data, and the many confounding factors in endemic disease surveillance, make it difficult to validate predictions of global change impacts on parasitic disease [82]. This explains the lack of well-documented, proven effects of global, including climate, change on disease incidence in livestock, which should not be taken to indicate the absence of such effects.

3.4. Sustainable Parasite Control

Ruminant production systems vary considerably, depending on social, economic and other environmental factors, such as soil, climate and farm structure. Predictable (and unpredictable) global changes will inevitably change the way these systems are operated [3]. These changes will also have both direct and indirect effects on helminth lifecycles (see above) and, thus, on the most appropriate preventative and remedial strategies required on farms.

Current chemically-based approaches to helminth control generally utilise frequent whole flock/herd treatments, even though these are known to lead to an increased rate of the development of anthelmintic resistance [85]. Additionally, there are societal concerns about the levels of chemicals present in food products. Although anthelmintic residue concentrations have been found to be very low in beef in Europe [86], concerns persist and underpin restrictions on anthelmintic use in livestock, especially in dairy cows [87]. In any event, the risk of AR is sufficiently serious that current chemical-based helminth control strategies can reasonably be deemed unsustainable unless considerably modified. Previous studies, reviewed in [85], have established proof-of-concept for *refugia*-based treatment strategies and have demonstrated the benefits of optimised anthelmintic usage in maintaining animal performance and drug efficacy, though mostly in small ruminants, rather than cattle. The ability to optimise treatments will likely change the way in which anthelmintics are used; they will only be given to those animals that actually need treatment, instead of, as is common practice now, treatment being given to all animals in a flock/herd simultaneously. Optimising drug treatments will slow the development of AR [88] and, thus, maximise the life of those anthelmintic families where resistance is known to be an issue and prolong the life expectancy of the two new sheep anthelmintic families, currently represented by monepantel [36] and derquantel [37]. Proof-of-concept studies so far published suggest that targeted whole-flock treatment or individual animal treatments are effective and pragmatic strategies for optimising anthelmintic use in Europe, as in a range of production systems across the world [63,85,89–94].

Targeted treatment (TT), *i.e.*, optimised whole flock/herd treatment, has been shown to be beneficial in controlling nematode infections, in both large and small ruminants. Targeted selective treatment (TST), *i.e.*, individual animal treatment, has been shown to reduce anthelmintic usage in small ruminants, whilst maintaining animal production and drug efficacy. However, to date, TST approaches have rarely been studied in cattle, and neither approach has been applied to liver fluke infections. The wide-scale uptake of these strategies can only be achieved with a full understanding of their potential costs and benefits; this has also not yet been properly evaluated, and the optimum balance between worm control and maintenance of efficacy in TST and Integrated Pest Control (IPC) programmes still needs to be identified. Current TT and TST strategies for small ruminants, for example, are most applicable for large-scale producers, because of the investment needed in efficient animal handling and

performance monitoring systems. Indicators of the need to treat at the group or individual level, which are easily applicable within smaller scale enterprises, are needed.

In order to make it possible to integrate these new strategies into routine farm management practices, farmers (and their advisors) will need to fully understand the costs and benefits of these novel treatment strategies. Previous studies [85] showed that TT and TST strategies can reduce anthelmintic use and maintain drug efficacy; however, there may be some increased costs associated with the use of the new strategies (such as increased labour and the costs of new technology and diagnostics). The economic costs and benefits of these more sustainable treatment strategies, in the short and long term, have yet to be rigorously analysed, with few specific studies [92], and the resulting uncertainty is perhaps the major obstacle to their adoption by livestock producers. This is compounded by the scarcity of hard data on the costs of anthelmintic resistance, as well as uncertainty regarding future access to new treatment compounds and their likely longevity in the face of selection for resistance.

Finally, to encourage the implementation of new treatment strategies into routine farm practices, decision support tools are needed. This is because targeted strategies are inherently more complex than universal protocol-based systems and must be flexible to differences in farm systems, climate and other context-specific factors [95]. Integration of decision support tools into pre-existing herd management software would help farmers to incorporate the ideas and approaches discussed above.

4. Conclusions

Anthelmintic resistance and global change are dominant factors underpinning current and future trends in parasitic disease in grazing ruminants. Climate warming acts on immature parasite stages outside the main host and could alter the level and timing of peak infection pressure. The way in which this translates to altered disease patterns is modified by many factors, including host immunity, grazing patterns and other farm management practices [96]. Meeting increased infection pressure with more frequent administration of anthelmintic drugs is unsustainable, due to rapid development of resistance in nematode and, probably, trematode populations. Therefore new approaches are required. Increasingly, the targeting of treatment at the group and individual level appears to be the only practical way forward for sustainable helminth control on farms. Much remains to be learned regarding the optimal design and implementation of such strategies in different contexts. We have outlined some of the challenges in this regard and identified key areas in which advances in science and technology can help to support effective and efficient strategies for maintaining productivity in the face of major future challenges. The adoption of improved parasite control practices is crucial for sustainable and efficient production from ruminants at pasture.

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Conflicts of Interest

The authors declare no conflicts of interest.

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