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Invited Review Article

Technological advances for sustainable helminth control in animal health amidst changing climate

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Abstract

Effective management of helminth infections in livestock plays a vital role in achieving sustainable livestock production and optimizing protein yields, particularly within the framework of climate change adaptation and efforts to lower greenhouse gas emissions. This paper explores comprehensive management strategies for helminth infections in domesticated ruminants, focusing on the complexities and potential solutions. It discusses advancements in diagnostic technologies, vaccines, selective breeding, and precision livestock farming (PLF) to enhance disease detection and control. Emphasis is placed on sustainable anthelmintic use and the search for novel compounds. Integrating these strategies supports the One Health approach, addressing the interconnected health of animals, humans, and ecosystems. This multidisciplinary approach aims to improve livestock health, productivity, and environmental sustainability, while tackling issues such as anthelmintic resistance and evolving helminth infection patterns influenced by climate, land use, and farming practices. Modern diagnostic technologies, including automated image processing and isothermal DNA amplification, alongside sensor and wearable technologies, enable real-time monitoring of animal health parameters and environmental conditions. These innovations promise enhanced disease control on farms, leveraging predictive modeling and innovative diagnostic markers for efficient disease management. This integrated approach facilitates timely intervention, ensuring sustainable livestock production and welfare enhancement through rapid, cost-effective diagnostics.

Keywords: Anthelmintic resistance, Climate change, Diagnostic technologies, Helminth infections, Innovative control approaches

Highlights

- Controlling helminths is crucial for sustainable protein production amid climate change.
- Explores strategies like diagnostics, vaccines, breeding, and PLF for improved disease control
- Discusses biosensors, wearables, and genomic tools for precise and efficient disease management
- Addresses resistance, evolving infections, and opportunities for innovative diagnostics
- Explores multi-species vaccines and proteomics for broader helminth protection in livestock

INTRODUCTION

Given the changing climate and the urgent requirement for sustainable development, it is essential to control animal diseases, namely helminth infections, in order to improve livestock output and fulfil the increasing demand for protein in the future. The need for this is amplified by the diminishing natural resource foundation for livestock production and the urgent need to decrease greenhouse gas emissions from the livestock industry. In order to meet the demands of our current social and economic environment, it is necessary to not only expand production but also adopt more efficient and ecological ways, all while guaranteeing the well-being of animals. To achieve these aims, it is crucial to effectively control helminth infections in livestock due to their widespread occurrence and negative impact on production efficiency. Throughout history and up to the present day, the management of helminth infections in livestock has predominantly depended on the use of chemotherapeutic agents for prevention or treatment. Nevertheless, as a result of their inherent genetic variability, helminths have continually developed strategies to avoid current methods of control, resulting in a growing prevalence of anthelmintic resistance (AR).

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Moreover, alterations in infection patterns are occurring due to shifts in climate, land use, and farming techniques, which are making control procedures more complex (Rose *et al*., 2015).

This paper attempts to provide a thorough approach to the management of helminth infections in domesticated ruminant animals by utilizing developments from several fields. The subsequent sections will examine the difficulties and suggested remedies in crucial areas. Initially, we will analyze the worldwide advancements in diagnostic technologies, which play a vital role in the precise identification and surveillance of diseases. Following that, we will explore novel control measures, such as the creation of vaccinations and the selective breeding of animals to enhance their resistance and resilience against helminths. In addition, we will evaluate the environmentally sustainable utilization of anthelmintics and the possible identification of novel compounds to attack these parasites. Lastly, we will discuss the logical incorporation of these upcoming control options into current management systems. This comprehensive approach is in line with the One Health idea, which emphasizes the interrelated health of animals, humans, and ecosystems, especially in relation to changing climate conditions. Our strategy seeks to not only boost animal health and productivity, but also to improve environmental sustainability and public health.

Tools for diagnosis

Advancements in diagnostic tools on a global scale: Improvements in diagnostic tools are crucial for effectively managing helminth infections. There is a significant technological revolution happening in the diagnostics industry, with the potential to extend to veterinary medicine in the future. Macroparasite infections differ from typical bacterial and viral infections in that the parasites do not reproduce inside the host organism. Consequently, the significance lies not solely in whether the animal is infected or uninfected, but rather in the level of infection, which refers to the quantity of infectious stages acquired and the extent of the established parasite load. Evaluating the intensity levels of parasite infection and their impacts on key production parameters is essential for identifying the most effective diagnostic tools.

Precision livestock farming (PLF): In the human health sector, established suppliers of diagnostic equipment, reagents, and services are facing competition from new players with a technology background. For example, with the advancement of wearable trackers and internet-connected devices, it is now feasible to consistently gather and analyze data to offer health guidance as we strive to advance in preventive medicine. An example of this is smart watches that collect data on various factors, such as movement patterns and body temperature, and utilize this information to provide advice or send early warnings to improve the user's health.

Precision livestock farming (PLF) is a revolutionary method of livestock management that incorporates cutting-edge technologies to improve animal health, welfare, and productivity. PLF provides advanced solutions for monitoring, preventing, and managing helminth infections in the field of ruminant helminth control. These solutions offer improved accuracy and efficiency in dealing with helminth infections. This note delves into the use of PLF technologies in controlling helminth infections in ruminants. It discusses the challenges associated with these infections and emphasizes the potential advantages for sustainable livestock management. The PLF incorporates cutting-edge diagnostic tools that enable fast and precise identification of helminth infections.

Biosensors and wearable devices are used to monitor physiological and behavioral changes in ruminants. They provide early indications of helminth infections. Automated fecal egg counting systems utilize advanced image analysis and machine learning techniques to accurately quantify parasite eggs in fecal samples. This cutting-edge technology allows for precise monitoring of infection levels, providing valuable insights for effective parasite control.

By utilizing advanced analytics and predictive modeling, data obtained from PLF systems can be effectively analyzed. This analysis enables the ability to forecast infection outbreaks, specifically predicting helminth infection patterns. This prediction is based on historical data, climatic conditions, and farm management practices.

Customizing anthelmintic treatments for individual animals or specific groups according to their infection risk minimizes unnecessary drug usage and addresses the development of anthelmintic resistance.

Automated systems, with their ability to continuously monitor various parameters concerning environmental and animal health, play a vital role. These parameters encompass assessing the contamination levels of helminth larvae in pasture conditions, which is essential for making informed grazing management decisions and monitoring animal behavior to identify potential health issues. This is achieved by tracking changes in grazing patterns, feed intake, and activity levels.

Genomic information is utilized by PLF to improve breeding programs focused on creating ruminant breeds that are resistant to helminths. Genomic selection is a powerful tool that allows for the identification of genetic markers linked to helminth resistance. This valuable information enables breeders to choose animals that are more resilient to helminth infections. By employing this technique, breeders can make better-informed decisions when selecting animals for breeding.

Precision breeding utilizes genetic data and advanced reproductive technologies to propagate traits that are resistant to various factors. Precision livestock farming offers a potential solution for improving helminth control in ruminants. Through the integration of cutting-edge diagnostics, data analytics, automated monitoring, and genomic technologies, PLF provides a solution that is both sustainable and highly efficient for managing helminth infections.

The FECPAKG2: It is a state-of-the-art fecal egg counting system that has been developed to improve the accuracy of diagnosing helminth infections in livestock. This technology utilizes digital imaging and automated analysis to deliver precise quantification of parasite eggs in fecal samples. FECPAKG2 enables efficient decision-making for parasite management by combining cloud-based data storage and real-time reporting (Rashid *et al.*, 2018). The methodological note discusses the advantages of using a simplified method for fecal egg counts, which eliminates the need for extensive labor and expertise. The user-friendly interface makes it convenient for on-farm use. The FECPAKG2 software promotes sustainable livestock practices by facilitating precise anthelmintic treatments, which in turn aids in the prevention of anthelmintic resistance and enhances the overall health and productivity of the herd.

Advances in immunological and DNA-based diagnostics: In addition, there have been numerous advancements in immunological and DNA-based diagnostic techniques, which have improved the sensitivity and cost-effectiveness of detecting parasites and potentially determining their abundance. These advancements have made it possible to implement semi-automated procedures in diagnostic laboratories, although they still necessitate significant labor or costly equipment. The digital revolution should lead to a shift towards fast, affordable, and precise point-of-care diagnostics, along with proper data storage to identify the animals or situations that require management intervention. In recent years, there has been a significant improvement in the accuracy and affordability of nucleic acid sequencing methods, such as second- and third-generation sequencing tools. Technological progress has led to the emergence of innovative platforms for analyzing whole genome and metagenome data, which have become more accessible for routine diagnostic applications across diverse medical disciplines. However, these technologies are not yet employed for the diagnosis of helminth infections in ruminants. Furthermore, developments in nanopore-based third-generation sequencing technology have facilitated the creation of portable sequencing devices, such as the MinION sequencer, which is compact enough to be housed within a USB flash drive. For instance, this technology allows for on-site collection of mass sequence data and has been demonstrated to facilitate analysis of bacterial metagenomes (Tyler *et al.*, 2018). At present, the error rates of third-generation sequencing methods remain high, with the expectation that they will be resolved in the coming years.

In addition, when it comes to identifying and distinguishing various helminth species, these error rates can be deemed acceptable. Methods for accurately measuring levels of parasite infection may still be under development, but one potential solution is to use binary outcomes that indicate a threshold for significant production loss. Therefore, it is likely that the detection of multiple pathogens on farms using nucleic acid analysis will be both technically and economically viable in the coming future.

By utilizing advanced farm sequencing tools, it becomes possible to identify and distinguish between various helminth species that infect individual animals. Additionally, these tools can also detect genetic traits linked to AR. Unfortunately, genetic markers for resistance are still lacking for most of the drug classes currently in use (Kotze *et al.*, 2020). Therefore, a significant improvement in our understanding of the fundamental molecular mechanisms of AR is necessary before we can accurately evaluate the information obtained through third-generation sequencing in relation to AR. Resistance against the macrocyclic lactones, which are widely used in ruminants, is a significant concern. It is important to note that these tests are not commonly used to monitor ruminant herds, and testing for AR is not regularly done using any method. It seems likely that this situation will remain the same unless AR testing becomes more affordable and convenient, and covers all major resistance mechanisms for relevant anthelmintic classes.

Proteomic analysis of biological material holds immense promise for future diagnostic applications in ruminants, enabling the detection of helminth infections. Regarding the analysis of parasitic helminths, Matrix-assisted laser desorption/ionization time-of-flight mass spectrometry MALDI-TOF MS has been utilized for identifying Trichinella spp., and there have been some preliminary findings for cyathostomins, which are the most common gastrointestinal helminths in horses (Feucherolles *et al.*, 2019). This technology offers the benefits of cost-effective sample analysis and dependable results. The analysis of a single crude protein extract enables the detection and differentiation of multiple species. Before implementing this technique, it is crucial to establish and validate it for the various helminth species found in ruminants. It is quite likely that, like the nucleic acid tools mentioned earlier, other significant bacterial and viral pathogens can also be identified simultaneously through the analysis of the same sample. At present, it remains uncertain whether it will be feasible to conduct quantitative proteomic analysis of helminth infections at a species level.

Ultimately, the identification of biomarkers, such as liver proteins, regulatory hormones, or acute phase proteins, holds significant promise for future health monitoring in ruminants, particularly in relation to helminth infection. There are several benefits to using biomarker detection tools. One advantage is the ability to use non-invasive sample matrices like saliva. Additionally, these tools allow for the assessment of multiple parameters and the detection of multiple pathogens in a single sample. For instance, this has been shown in the case of helminth infections in cattle. A magnetic bead-based multiplex assay has been created to detect these infections simultaneously (Karanikola *et al.*, 2015).

Translating modern diagnostic technology for the management of parasitic diseases on farms: Although laboratory-based tests primarily concentrate on diagnosing species at the population level, there will also be a requirement for on-farm diagnostics that can serve as real-time decision-making tools. Initially, conventional diagnostic methods such as analyzing faces, serum, or milk can be integrated with innovative technology like automated picture processing (e.g., utilizing smartphones) and isothermal DNA amplification. This method has the benefit of identifying and measuring helminth eggs or a diagnostic test reaction without requiring the expertise of interpreting images or findings (Jiménez *et al.*, 2016). Additionally, sensors can be placed in the animals' surroundings to assess their movement, sound, or other variables. In the case of helminth infections transmitted through pastures, the use of sensor networks can help monitor meteorological and environmental conditions. By combining this data with prediction models of parasitic disease transmission, farmers can be alerted when the infectivity levels on the pastures go over specific thresholds. Significant progress is expected to be made through the use of sensors and wearable technology that can be directly inserted into or attached to animals. This development aligns with the aforementioned trend in monitoring human health. These sensors have already been developed to identify the components of perspiration, assess body temperature, monitor behavior and movement, detect stress, analyze sound, and measure pH levels. The field of helminth control has already investigated several hypotheses that could considerably benefit from these revolutionary technologies. For example, gastrointestinal parasitism has been observed to change grazing behavior. Behavioral changes, such as variations in location or activity, can serve as valuable indicators for diagnostic purposes. Studies have demonstrated that animal movement or sound analyzers are capable of detecting coughing in grazing animals, potentially signaling lungworm infection. Moreover, these analyzers can identify animals that have grazed in areas contaminated with liver fluke metacercariae, aiding in targeted disease management. Additionally, these analyzers can determine which animals have been grazing in areas contaminated with liver fluke metacercariae. Another method for monitoring parasitic gastritis and optimizing feeding regimens is by using a wireless pH sensor in the abomasum, as demonstrated by Weinstein *et al.* (2013). The diagnostic markers of parasite infection, which are now detectable in milk, saliva, or feces (Sawangsoda *et al.*, 2012), will be assessed in sweat and may achieve a higher degree of convenience. In summary, the implementation of rapid, cost-effective, and precise point-of-care diagnostics will allow for immediate detection of highly infected animals. This will facilitate prompt treatment to sustain production or the removal of such animals from the breeding population.

Innovative control approaches

Role of Toll-like receptors in inducing resistance to parasitic agents: Gastrointestinal nematode (GIN) infections considerably affect the productivity of small ruminants globally, with resistance differing among breeds as a result of genetic influences. Toll-like receptors (TLRs) are essential elements of the innate immune system, crucial for the identification of pathogen-associated molecular patterns (PAMPs) on parasitic agents and the initiation of immune responses. Toll-like receptors (TLRs) activate a series of immune signaling pathways that improve the host's capacity to resist or tolerate gastrointestinal nematode (GIN) infections.

In ruminants, particular polymorphisms in TLR genes correlate with differences in immune responses to helminths. TLR2 and TLR4 play a significant role in the recognition of glycoproteins and lipopolysaccharides derived from parasites, leading to the activation of downstream cytokine production. Cytokines such as interleukin-4 (IL-4) and interferon-gamma (IFN-γ) enhance the differentiation of T-helper cells (Th2), facilitating protective mechanisms including augmented mucosal immunity and the expulsion of parasites.

Alim *et al*. (2016) discovered 31 single nucleotide polymorphisms (SNPs) in goat Toll-like receptor (TLR) genes, of which nine were substantially correlated with susceptibility to *Haemonchus contortus* infection. Four notable haplotype blocks were identified, with block 6 associated with an increased risk of infection. These mutations may impact the structure and function of TLR, hence influencing immune responses to gastrointestinal nematodes. Understanding the modulation of TLRs and their signaling pathways can inform the creation of genetically resistant breeds and novel immunotherapeutic approaches for sustainable helminth control, especially in the context of climate change challenges.

Vaccination: There is a limited number of helminth vaccinations available for animals. Currently, the available vaccines for nematodes are limited to the cattle lungworm (*Dictyocaulus viviparus*) vaccine (Bovilis® Huskvac, MSD Animal Health) and a vaccine for the barber's pole worm (*Haemonchus contortus*) in sheep (Barbervax®, Wormvax Australia Pty Ltd). Significant progress is underway in the development of experimental vaccines targeting various helminth species in livestock, including *Teladorsagia circumcincta* in sheep, *Ostertagia ostertagi* and *Cooperia oncophora* in cattle, and the liver fluke *Fasciola hepatica* in ruminants. These advancements lay the foundation for expanding the range of effective control measures against parasitic infections in livestock. Several crucial technological challenges must be addressed before the majority of these experimental vaccinations may be transformed into marketable pharmaceuticals. The transition from protective native (glyco-)proteins to recombinant or peptide-based vaccines should be prioritized for development. There are currently only two commercially available vaccinations for helminth parasites that have been genetically modified. One is used to protect ruminants, such as cows and sheep, from *Echinococcus granulosus*, and is called Providean HidatilEG95®. The other vaccine, called Cysvax®, is used to protect pigs from *Taenia solium*. Considering the swift advancements in proteomics and glycomics technologies, it is plausible to anticipate the availability of more helminth vaccines, either recombinant or synthetic, in the coming future. Advancements in understanding host-parasite interactions will significantly drive the improvement of antigen delivery systems (Wu *et al*., 2019). Current vaccines targeting viral and bacterial pathogens are employed either as part of official disease control programs to address widespread diseases, such as vaccines for bluetongue virus (Bhanuprakash *et al*., 2009), or by individual farmers to prevent diseases and associated production losses, for instance, vaccines against neonatal bovine diarrhea (Maier *et al*., 2022). However, policymakers are unlikely to mandate the use of helminth vaccines, as helminth infections in livestock are classified as "production diseases", lacking significant implications for public health or international trade (Charlier *et al*., 2020). Hence, the farmer will have the duty of deciding whether to vaccinate, taking into account factors such as the vaccine's efficacy and cost-effectiveness in relation to other methods of control. Vaccine safety is a significant concern. The development of a potentially effective human hookworm vaccine utilizing activation-associated secreted proteins (ASPs) was halted due to severe allergic reactions observed in individuals previously exposed to the vaccine (Diemert *et al*., 2012). The necessary effectiveness and length of protection will vary based on the relationship between the host and parasite, as well as the practices used in farming, both of which are affected by the climate and environment. In places with limited grazing, short-term protection may be sufficient for gastrointestinal nematodes in cattle.

It is necessary to employ diagnostics that are easy to use and understand in order to identify animals that do not respond well to vaccination. This will enable the administration of anthelmintics or the removal of these animals from the group. It is desirable for future vaccines to provide protection against numerous species of helminths that impact grazing animals using a single product. These helminths may include various species of gastrointestinal nematodes or a combination of gastrointestinal nematodes together with lungworms and/or liver flukes. Nevertheless, monovalent vaccines can be advantageous in scenarios where a single parasite species prevails (such as *H. contortus*), when other parasites are managed through alternative methods, or in regions with a low risk of other parasites (such as liver fluke, which has an uneven spatial distribution). Helminth vaccines have the potential to be integrated with vaccinations targeting other infections. However, Vaccines targeting multiple pathogens are particularly advantageous when designed to address common disease complexes. For instance, neonatal bovine diarrhea can be managed with a combined vaccine targeting Escherichia coli, rotavirus, and coronavirus, while the bovine respiratory disease may be mitigated using a vaccine against pathogens such as bovine respiratory syncytial virus, parainfluenza virus, and *Mannheimia haemolytica*. On the other hand, parasitic gastroenteritis and husk are well-established diseases in grazing ruminants, and thus the inclusion of gastrointestinal nematode or lungworm antigens in vaccines alongside bacterial or viral antigens may offer limited additional benefit. The comprehensive integration of animal resistance has enhanced resilience against parasites on farms over the past forty years, and there has been considerable interest in the idea that farmed animals have an innate, genetically determined resistance to parasites (Emery *et al*., 2016). In intensive farming systems, exploiting this trait is common practice. Initial studies focused on genetic variations within individual herds and flocks, exploring the natural ability of animals to resist and recover from parasitic infections, particularly in highly developed farming systems. There is potential to utilize breed-specific resilience in these intensive systems as well.

Early selection criteria for breeding focused on nematode fecal egg counts (FECs), which have low heritability. However, more promising approaches using IgA-based methods and other molecular indicators for host resistance to various gastrointestinal nematodes have emerged. Despite the recognized importance of resistance and tolerance to parasites in future control efforts, implementing these concepts in the field remains challenging. Breeding for enhanced immune responses may not always be economically viable, as it can result in trade-offs with other valuable traits, such as growth rate and milk yield. Alternatively, selective breeding for resilience may inadvertently increase disease prevalence among less resilient individuals due to elevated infection pressures in shared grazing environments. For the widespread adoption of breeding for resilience and/or resistance (RR) in commercial farms, several obstacles need to be addressed. One major issue is measuring the trade-offs between production parameters and immunological efforts to enable comprehensive cost-benefit evaluations. Another involves balancing resource allocation between combating macroparasites and other pathogenic organisms common in intensive farms. Efforts to maximize production parameters often result in undesirable consequences. For example, the dairy industry's focus on milk production has led to decreased fertility and animal welfare, ultimately impacting farm profitability.

Additionally, milk from cows that graze on pastures yields superior cheese and butter compared to cows that are confined and fed, with grass-based milk containing higher amounts of beneficial lipids and antioxidants. Recognizing that animals should be bred for optimal, not maximal, output levels within specific production systems, breeding programs have integrated other traits, such as improved fertility. A novel system for assessing cattle's genetic potential for immunological response has been developed, but a lack of cohesion in studies has hindered determining the most effective energy allocations in farming systems.

To ensure farm animals effectively manage their energy requirements, a comprehensive farm-wide approach is necessary. This involves enhancing food uptake capacity, improving food quality, and increasing opportunities for food intake. Energy acquired will be allocated to growth, milk production, reproduction, and immunological functions. While previous research explored relationships between factors like lameness and milk output or food quality and worm load, a whole-system analysis is essential (Green *et al*., 2014). Selective breeding for resistance is practical in environments with a consistent supply of high-quality nourishment, but not if issues like lameness are not simultaneously managed. A big data approach, leveraging statistical advancements and modern computational capabilities, is required to breed the most efficient production animals for specific farm systems.

Anthelmintics: These are medications used to treat and prevent infections caused by parasitic worms. Due to their high effectiveness and ease of application, the control of worms globally has mainly depended on the use of anthelmintics. Since the 1990s, anthelmintics have primarily been utilized as tools for production rather than for therapy guided by diagnosis. The increasing affluence in developing countries has driven a higher demand for meat protein; however, the limited availability of land has constrained traditional livestock production. This scenario, combined with intensified parasite control measures, has contributed to the global emergence and spread of drug-resistant helminth populations, significantly jeopardizing the anticipated cost-effectiveness of these efforts.

The future discovery of anthelmintics: Future efforts in the discovery of novel anthelmintics are expected to persist, expanding to encompass a wider range of potential sources, including the investigation of medicinal plant extracts. However, the ongoing consolidation of the animal health industry has led to a reduction in resources allocated to anthelmintic research and development. As a result, the availability of new products may decrease, but their distribution is likely to be more carefully managed. Despite investments in alternative methodologies, empirical research remains the fundamental basis for discovering anthelmintic agents. Historically, the most effective approach has been administering experimental chemicals to parasite-infected animals and then assessing changes in parasite loads through necropsy. This process, however, is labor-intensive, time-consuming, and resource-demanding, leading to its decline in recent years. Additionally, the '3R' principles (Replacement, Reduction, and Refinement) are gaining priority in scientific research, promoting alternative methods that do not involve animals.

The process of drug discovery in parasitology has significantly changed over the last century. Technological advancements have led to a greater focus on mechanism-based drug development methods. This trend is expected to continue, improving assay efficiency and data quality. Advances in molecular biology and material-handling technologies have revolutionized the pharmaceutical industry's approach, transitioning from traditional phenotypic or whole-organism screening methods to highly efficient mechanism-based screening strategies. These modern approaches focus on specific protein targets rather than broader biological outcomes, leveraging detailed knowledge of anthelmintic mechanisms of action to enhance drug discovery. This understanding has enabled the anticipation of medication combinations to broaden effectiveness and impede antibiotic resistance progression.

Despite the strategic shift, the limited financial returns from investments in anthelmintic research have driven a renewed emphasis on high-throughput screening systems. These systems focus on utilizing accessible life stages of key parasites in phenotypic screening formats to optimize discovery efforts. Advancements in phenotypic screening procedures will further enhance the possibilities for discovering new anthelmintic drugs. Recent investigations have validated the efficacy of utilizing specific parasitic larvae in conjunction with the microfluidic electropharyngeogram (EPG) platform. This cutting-edge technique enables precise monitoring of the pharyngeal pumping activity of parasitic nematodes, providing critical insights into their feeding behavior and physiological responses. The integration of microfluidic technology with EPG enhances the resolution and accuracy of electrophysiological recordings, facilitating detailed studies on the pharmacological effects of anthelmintics and representing a significant leap in parasitological research (Weeks *et al*., 2018).

Several new drugs for treating parasitic worms in animals have become available recently, including cyclic depsipeptides (e.g., emodepside), amino-acetonitriles (e.g., monepantel), and paraherquamides (e.g., derquantel). Other similar drugs are likely under development. However, insufficient data hinder a thorough investigation of the reasons for the lack of success of mechanism-based approaches in parasitology (Geary, 2012). Several obstacles, including the difficulty of achieving functional expression of parasite proteins suitable for assays and extrapolating activity observed in protein-based assays to complete organisms, hinder the feasibility of conducting mechanism-based screenings for antiparasitic medications. The current lack of successful outcomes in anthelmintic research raises questions about whether this is due to suboptimal goal selection, inadequate financial investment, or a fundamental flaw in the underlying strategy. Advancing our understanding of the basic biology, biochemistry, and physiology of parasites is likely to enhance the success rate of drug discovery efforts. However, the simplicity and efficiency of conducting extensive phenotypic screens ensure the continued use of this unbiased approach. Additionally, 'repurposing' screens-where compounds effective against established molecular targets in other organisms, such as insects or mammals, are evaluated against parasitic helminthes-offer a promising avenue for accelerating the identification of new, effective compounds.

Prospects of natural products in combating helminth infections: Scientific studies have verified that bioactive forages, such as plant cysteine proteinases, flavonoids, and condensed tannins, possess anthelmintic properties. These characteristics have been observed in both small ruminants and cattle. In the past two decades, approximately 850 scientific publications have focused on the use of natural chemicals to combat helminths. Research has shown that condensed tannins, along with flavonoids like quercetin and luteolin, have a synergistic effect in suppressing the ex-sheathment of *Haemonchus contortus* L3 larvae in laboratory settings. These findings suggest that combining plant materials containing these components or selecting plants with high levels of tannins and flavonoids could enhance anthelmintic efficacy. Crude mixes of natural materials are likely to affect different pathways in worms compared to the routes targeted by conventional anthelmintics, potentially eliminating nematodes that have developed resistance to existing treatments. Incorporating bioactive forages into livestock diets presents dual benefits, offering both anthelmintic and nutritional advantages due to the presence of plant secondary metabolites (PSMs) with anthelmintic properties. This approach aligns with the nutraceutical concept, which involves dietary compounds that contribute to health improvement, including disease prevention and treatment. Globally, efforts are advancing toward the development of nutraceutical products for helminth control in ruminants across various livestock production systems. However, the majority of natural compounds remain insufficiently studied, with limited scientific evaluation of their efficacy, mechanisms of action, and the precise identification of active components. Consequently, there is currently no commercially available plant-derived anthelmintic. Obstacles to widespread use include difficulties in registration, lack of familiarity with mechanisms of action, the presence of interacting secondary metabolites, potential toxicity, concerns about residues, quality assurance issues, and challenges in manufacturing and distribution.

Role of nutrition and parasite interaction

Nutrition plays a pivotal role in the interaction between host animals and parasites, influencing both the severity of parasitic infections and the effectiveness of control measures. Parasites, especially gastrointestinal nematodes, impair animal health by affecting appetite, gut function, and nutrient metabolism. In particular, a well-balanced diet can enhance the host's ability to resist or recover from parasitic infections by bolstering immune responses and improving overall health. Nutritional strategies, such as increasing protein and energy intake, can significantly aid in the animal's recovery, reduce parasite burdens, and mitigate the negative effects of parasitism (Bricarello *et al*., 2023).

Furthermore, the addition of specific micronutrients, such as vitamins and minerals, plays a key role in supporting immune functions and reducing susceptibility to infections. For example, minerals like copper, selenium, and phosphorus are known to enhance host resistance to parasitic infestations (Abbas *et al*., 2023). This nutritional approach not only supports animal health but also provides an environmentally sustainable alternative to conventional chemical treatments.

Ultimately, integrating nutritional interventions into parasite management strategies offers a promising route for reducing dependence on anthelmintics while improving the long-term health and productivity of livestock, particularly in organic and sustainable farming systems.

The future of anthelmintic use

In the future, anthelmintics will continue to be essential, but their usage will transition from regular applications to more focused therapeutic interventions. The implementation of novel control techniques and sophisticated diagnostic tools will allow for targeted administration of treatments exclusively to animals requiring them, at the most opportune moments. This will mark the advent of a revolutionary age in the application of anthelmintics. It is crucial to acknowledge that if anthelmintics are used for therapeutic purposes instead of preventive purposes, it may decrease the number of dosages sold. This might potentially limit the motivation for investing in new discoveries. Targeted therapy may warrant the use of more costly products, considering that the cost of treating severely damaged animals would surpass the costs of unneeded treatments currently given to unaffected animals. This alteration may also decelerate the emergence of anthelmintic resistance (AR) to novel medications, therefore prolonging their effectiveness. In terms of the industry, it is expected that future anthelmintic solutions, whether they include a single active ingredient or numerous ones, will be incorporated into comprehensive management programmes. Regulatory agencies are expected to impose stricter regulations to minimize environmental contamination and food residues, restricting the use of anthelmintics to cases where diagnostic evidence confirms the presence and significance of helminth infections. These restrictions will encourage the use of effective methods to manage parasites and may also encourage the development of new and improved treatments. In the future, we expect the development of novel anthelmintics and combination products, as well as a substantial change in worm management tactics for ruminants. New diagnostic techniques will enable more accurate treatments, vaccinations will be accessible, and highly heritable immunological biomarkers will be identified and used in selection programmes. This will decrease dependence on regular use of anthelmintics for the entire herd. In order for these improvements to be successfully integrated into agricultural practices, it is crucial to effectively convey the information to farmers and veterinarians and ensure that they are economically viable. Hence, enhancing the knowledge of these individuals will be crucial in order to bolster future control endeavors.

Rational integration for future helminth control practices

Historically, helminth control strategies have focused primarily on reducing parasite burdens and enhancing productivity by developing novel, more effective, or easier-to-use methods. Recently, however, there is an increasing emphasis on the environmental impact of livestock production and animal welfare. Livestock production affects the environment through resource utilization and pollution, with these external costs not fully reflected in the prices paid by producers or consumers. These externalities impact the welfare and opportunities of others without direct compensation. Effective helminth control can help address these challenges. For instance, liver fluke infestations in cattle can increase greenhouse gas emissions by up to 10% per affected cow (Jonsson *et al*., 2022). The implementation of effective anthelmintic strategies can help reduce greenhouse gas emissions at the farm level. While the impact on water use is yet to be fully assessed, it is likely beneficial due to reduced thirst in animals suffering from protein-losing gastroenteritis.

Conversely, helminth control also has downsides, such as increased labor input, the development of anthelmintic resistance (AR), and the leakage of residues into the environment or food products. Future decision-making in helminth control will increasingly need to consider all these factors. Current economic evaluations typically assess the cost of helminth diseases or conduct cost-benefit analyses of specific interventions at the farm level. New methodologies are emerging that include indirect effects in decisions about managing endemic helminth infections. Recent approaches position gastrointestinal nematode infections and their control measures within the broader context of whole-farm economics. This perspective connects disease management and mitigation strategies to both the inputs and outputs of a production system, facilitating the benchmarking of farm performance against industry peers.

These methods will increasingly assist in helminth control decision-making at the individual farm level and can also be leveraged by governments and regulators to evaluate impacts, even in the absence of known market values, as long as standardized output measures are available. Environmental performance and animal welfare scores are becoming more accepted as criteria. Currently, product market authorization mainly evaluates safety, quality, and efficacy, but these new methods will enable consideration of broader impacts on the ecological footprint and animal welfare. The application of these methods depends significantly on scientific data, which are often lacking or require further validation across various regions or production settings. Only through progressively enhancing our understanding of the economic, social, and environmental impacts via experiments and surveys, and integrating this knowledge into whole-system approaches, can intervention strategies be optimized in a comprehensive and holistic manner.

Role of 'Refugia' in managing the problem of resistance

The concept of 'refugia' involves leaving a portion of the parasite population unexposed to anthelmintics, typically by not treating all animals in a group. This strategy preserves drug-sensitive parasites, which dilute the progeny of resistant parasites, thereby slowing the development of resistance. Refugia-based control has been emphasized since van Wyk's 2001 proposal, advocating its integration into sustainable parasite management practices (Hodgkinson *et al*., 2019).

Targeted selective treatment (TST) exemplifies this approach, wherein only animals with high fecal egg counts (FEC) are treated. By leaving approximately 20% of the flock untreated, sensitive worms continue reproducing, reducing the dominance of resistant alleles in the population. This method is particularly effective when resistance is at a low level. Refugia reduces selection pressure by limiting contact between the drug and the entire parasite population, thereby extending the efficacy of available anthelmintics and ensuring long-term parasite control in livestock systems.

Modelling

Parasite modeling for control involves creating mathematical or computer representations of the interactions between parasites and their hosts. These models help forecast parasite behavior, transmission patterns, and the effects of various control techniques. Important considerations include understanding life cycles, reproduction rates, and environmental impacts. Models can incorporate information about host immunity, migration patterns, and treatment efficacy. By simulating numerous scenarios, they identify optimal intervention points and potential outcomes, aiding in the development of targeted medications, vaccination strategies, and public health regulations.

Effective modeling requires interdisciplinary collaboration, combining biology, epidemiology, and statistics to enhance parasite control and mitigate disease impact. Utilizing socio-psychological models to understand farmers' decision-making regarding parasite control and developing efficient communication strategies can help stakeholders adopt new technologies and make informed choices (Jack *et al*., 2017). By examining parasite transmission patterns and the effects of intervention strategies on epidemiology, calf growth, and farm economy, researchers can support the effective integration of parasite control into overall farm management.

Predictive models serve three primary purposes: understanding fundamental processes applicable across systems, analyzing specific system interactions that contribute to disease patterns and potential interventions, and providing precise control recommendations for individual farms. Advances in computational capabilities, Precision livestock farming (PLF), and data from livestock monitoring and health assessments are expected to enhance the role of computer models in sustainable parasite management.

Mathematical models have significantly improved our understanding of parasite population dynamics and will continue to provide valuable insights. Theoretical frameworks explain how nutritional resource allocation impacts parasite tolerance, aiding in comprehending the interaction between nutrition and parasites. These frameworks have been integrated into system-specific models and used in interventions like breed selection (Bishop and Stear, 2003).

Adding complexity to general models in agricultural settings can hinder analytic solutions, often requiring computer simulations to compare scenario outcomes. Helminth transmission is spatially driven by livestock movement and climate effects on free-living stages, necessitating assumptions about common farm management practices. Simulation models must adapt to varying climates and practices, requiring further adjustments to assess future agricultural conditions.

Specific models addressing issues like anthelmintic resistance (AR) must incorporate assumptions about farm practices and AR genetics, which can be limiting. However, detailed models are essential for understanding the effective application of new control tools. These models can establish specific goals for interventions, assist in experiment design, and provide empirical evidence to validate model outputs.

General patterns in farm management vary significantly and are influenced by factors not fully understood. Thus, general model outputs provide strategic guidance but may lack precision for direct farm-level decision support. Integrating computer power with high-throughput diagnostic tests and sensors will be crucial for effective parasite management in the near future. Automation of data gathering and model calibration will optimize control procedures, enhancing production efficiency and sustainability.

Implementing these advancements requires incorporating new tools into evolving farm management and climatic settings. Understanding host-parasite interactions beyond current knowledge will necessitate in silico methods to explore farm-host-parasite system interactions and outcomes. Integrating parasite control into comprehensive farm management will involve considering new technologies, socio-economic frameworks, environmental factors, and animal welfare. Farmers need realistic expectations of new tools, which require investments in time, costs, and training, while researchers must simplify new technologies to enhance accessibility. Expanding this field's scope to diverse cattle production conditions, especially in poorer regions, is essential for global impact.

Frogin' as a forecasting module for helminth infections

Frogin' is an innovative forecasting tool designed to predict and manage helminth infections in livestock by integrating environmental, host, and parasite parameters for precise infection risk predictions. It uses climate data such as temperature, humidity, and rainfall to model conditions favorable for helminth survival and transmission while considering host factors like grazing behavior, immune responses, and parasite loads to anticipate infection patterns. The module provides real-time, actionable forecasts to guide strategic interventions, including targeted anthelmintic treatments and grazing management, promoting sustainable parasite control. By encouraging judicious use of anthelmintics, Frogin' reduces selection pressure, slows the development of resistance, and ensures long-term efficacy of control strategies. This location-specific and time-sensitive approach enhances livestock health, productivity, and economic outcomes for farmers while contributing to sustainable helminth management.

Advancements in helminth control technologies: Addressing current limitations and future directions

Despite significant advancements in technologies for helminth control in livestock, several research gaps remain that hinder the full realization of these innovations. While current strategies emphasize the importance of sustainable anthelmintic use, diagnostic technologies, and vaccines, several key areas need further exploration:

Anthelmintic resistance management: The rise of anthelmintic resistance remains a pressing issue. Further research is needed to develop and integrate novel compounds and alternative control methods that can mitigate resistance and enhance the efficacy of treatment strategies.

Diagnostic technology integration: While advancements such as biosensors, wearable devices, and genomic tools have been made, the practical implementation and integration of these technologies into routine farm practices require additional development. Research should focus on optimizing these technologies for real-time monitoring and ensuring their accessibility and affordability for farmers.

Vaccine development and deployment: Although experimental vaccines show promise, challenges remain in converting protective native proteins into effective recombinant or peptide vaccines. More research is needed to address technological challenges, improve vaccine efficacy, and explore the potential for multi-species vaccines that offer broader protection.

One Health approach implementation: The integration of helminth control strategies with the One Health approach requires more in-depth investigation. Research should aim to better understand the interconnected health of animals, humans, and ecosystems to develop holistic and sustainable solutions.

Policy and economic considerations: The current focus on "production diseases" limits the adoption of vaccination programs. Research should explore the economic viability of helminth vaccines and address safety concerns, including those related to human health, to support more widespread adoption and policy changes.

Addressing these gaps will be crucial for advancing sustainable helminth control in the context of climate change and enhancing livestock health and productivity.

Conclusion

Controlling helminth infections in livestock is essential for improving productivity and sustainability amid climate change and rising protein demand. Current dependence on chemotherapeutic agents faces challenges from increasing anthelmintic resistance and evolving infection patterns. Advances in diagnostic technologies, such as biosensors, wearable devices, and genomic tools, provide precise and efficient solutions. Precision Livestock Farming (PLF) incorporates these technologies for enhanced monitoring and management. Future diagnostic innovations, including proteomic analysis and on-farm real-time diagnostics, promise further improvements. Embracing these advancements will enhance animal health, productivity, and environmental sustainability, aligning with the One Health approach. Currently, only two helminth vaccines, Bovilis® Huskvac for cattle lungworm and Barbervax® for sheep's barber's pole worm are available. Experimental vaccines for species like *Teladorsagia circumcincta*, *Ostertagia ostertagi*, *Cooperia oncophora*, and *Fasciola hepatica* show promise. Technological challenges, such as the conversion of protective native proteins into effective recombinant or peptide vaccines, must be addressed. Two genetically modified vaccines, Providean HidatilEG95® (for *Echinococcus granulosus* in ruminants) and Cysvax® (for *Taenia solium* in pigs), are currently in use. Advances in proteomics and glycomics indicate that the future development of more recombinant or synthetic helminth vaccines is promising. However, policymakers may not mandate helminth vaccinations due to their classification as "production diseases", leaving vaccination decisions to farmers based on efficacy and cost-effectiveness. Safety concerns, such as those observed in human hookworm vaccine trials, remain critical. The ultimate goal is multi-species vaccines for broader protection in grazing animals, potentially integrated with other disease vaccines.

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