

## Feature Review

## 100 Questions in Livestock Helminthology Research

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**An elicitation exercise was conducted to collect and identify pressing questions concerning the study of helminths in livestock, to help guide research priorities. Questions were invited from the research community in an inclusive way. Of 385 questions submitted, 100 were chosen by online vote, with priority given to open questions in important areas that are specific enough to permit investigation within a focused project or programme of research. The final list of questions was divided into ten themes. We present the questions and set them briefly in the context of the current state of knowledge. Although subjective, the results provide a snapshot of current concerns and perceived priorities in the field of livestock helminthology, and we hope that they will stimulate ongoing or new research efforts.**

### Towards Inclusive Identification of Research Priorities

The study of the helminth parasites of livestock is facing a period of rapid change. The availability of a series of highly effective and affordable **anthelmintics** (see [Glossary](#)) from the 1960s onwards coincided with the intensification of animal production systems in many parts of the world. As a result, adequate control of helminths could be achieved on the majority of farms with existing scientific knowledge, reducing incentives for investment in further research [1]. Currently, however, the effectiveness of control is breaking down in various areas. **Anthelmintic resistance (AR)** is increasing worldwide in helminths of all livestock species, highlighting the reliance of modern food production on chemical control of pests and parasites, and threatening the sustainability of livestock production, especially in grazing systems [2–4]. At the same time, changes in weather and climate are making infection patterns less predictable, and fixed protocol-driven approaches to helminth control are consequently less reliable [5]. To counter these challenges, alternative methods for helminth control are being developed, including, for example, vaccines, **biological control**, **bioactive forages**, grazing management, selective breeding, and various ways of targeting treatment in response to indicators of parasite infection or its impacts [6]. Development and effective application of novel control approaches require a return to fundamental scientific research to underpin future advances in parasite management. This renaissance of interest in veterinary helminthology comes at a time when it might profitably harness an explosion of new technologies, arising from rapid advances in molecular biology and ‘omics’, predictive modelling and data mining, sensor technologies, and other fields [1].

### Highlights

Important questions on helminths of livestock were elicited across the research community and prioritised by online vote.

The approach contrasts with traditional review formats and seeks to identify questions agreed to be both important and feasibly addressed by focused research projects.

A shortlist of 100 questions is presented with supporting text to provide perspective.

The article is intended to stimulate new and ongoing research on helminth infections, in support of sustainable global livestock health and productivity.

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In order to address research challenges and opportunities in relation to animal diseases, including those caused by helminths in livestock, new formal groupings serve to augment existing collaborations and provide a platform for coordination, mainly at European level (Box 1). In some, experts are enlisted in structured gap analyses to stimulate research and feed into priority-setting by funders and policy makers, as well as produce published outputs [7,8]. In other cases, experts produce opinionated reviews on the state of the art and expound a vision of the way forward [1,4,9]. These exercises are built on consensus, often among those who have worked together over a sustained period to develop ideas and drive progress in the field. While these approaches are undoubtedly useful, they tend to perpetuate dominant current thinking, and potentially neglect marginal but promising suggestions.

Alternatives are possible. Inspired by previous attempts in ecology [10], we here consult more widely across the research community to identify key current questions in livestock helminthology, to motivate and guide new work. The number 100 was chosen such that questions might be broad enough to be strategically important, yet focused enough to be tackled within a single focused research project or programme [10]. We elicited questions from as wide a base as possible within the discipline (Box 2), to reduce the influence of expert views and established dogmas on the questions presented, and to allow for disruptive and creative ideas. Further

#### Box 1. Initiatives to Identify and Prioritise Research Needs on Livestock Diseases in Europe

Deciding where public and private research spending will have the greatest impact is a complex process involving multiple interests. Often, *ad hoc* expert groups are created to provide decision makers with advice over specific topics. In addition, over the last decade several initiatives have emerged at European and global levels to foster international discussions and apply a structured approach to the identification of research gaps and priorities in the animal health domain, including livestock helminthology in Europe.

**DISCONTOOLS**<sup>v</sup> is a publicly funded, open-access database to assist public and private funders of animal health research and researchers in identifying research gaps and planning future research [104]. The database contains research gaps as well as a gap-scoring and prioritization model for more than 50 infectious diseases of animals. The information is provided by disease-specific expert groups and updated on a 5-year cycle.

The DISCONTOOLS database acts as a key resource for the **STAR-IDAZ** International Research Consortium on animal health<sup>y</sup>, comprising research funders and programme owners from Europe, Asia, Australasia, the Americas, Africa, and the Middle East, as well as international organisations, and includes representation from veterinary pharmaceutical companies. Members coordinate their research programmes to address agreed research needs, share results, and together seek new and improved animal health strategies for at least 30 priority diseases, infections, or issues. These include candidate vaccines, diagnostics, therapeutics and other animal-health products, procedures, and key scientific information, and tools to support risk analysis and disease control. STAR-IDAZ develops road maps on how to achieve these new animal-health strategies.

The **Animal Task Force (ATF)**<sup>vi</sup> is a European public-private platform that fosters knowledge development and innovation for a sustainable and competitive livestock sector in Europe. It represents key stakeholders from industry, farmers, and research from across Europe. It is a knowledge-based lobby organisation working at the forefront of livestock-related issues in Europe, including but not limited to animal health issues. The ATF unites members from every aspect of the livestock value chain (from feeding and breeding to production and processing), enabling an integrated approach to contribute to the environmental and societal challenges of livestock systems.

The **Livestock Helminth Research Alliance (LiHRA)**<sup>vii</sup> is a consortium of researchers that aims to develop sustainable effective helminth-control strategies and promote their implementation by the livestock industry. LiHRA grew out of EU-funded research projects addressing challenges in the control of gastrointestinal nematodes (FP6 PARASOL) and liver fluke (FP6 DELIVER) in ruminants under global change (FP7 GLOWORM), and related projects investigating alternative control approaches (Marie-Curie Initial Training Networks NematodeSystemHealth, Healthy Hay and Legume Plus<sup>viii</sup>). LiHRA meets annually to review current challenges, recent results and opportunities for collaborative research. Discussions within LiHRA gave rise to the current article, and also underpinned the EU-funded networking COST Action COMBAR.

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### Box 2. An Inclusive Bottom-up Elicitation of Research Priorities: Approach and Outcomes

The questions presented in this article were elicited in a way intended to be inclusive and to encourage participation from a diverse range of researchers, regardless of career stage, gender, or geographic location. Initially, LiHRA members (Box 1) were introduced to the concept by oral presentation at their annual meeting in 2016 and asked to submit questions in hard copy or by email; this request was repeated by email to the wider alliance membership. A total of 151 questions were submitted in this way from 17 members, all based in Europe. To broaden geographic inclusivity, members were asked to forward the link to a simple online survey through their international networks, which introduced the exercise and requested questions by free text entry. An oral presentation was also made at the 26th biennial international conference of the World Association for the Advancement of Veterinary Parasitology (WAAVP)<sup>ix</sup>, held in 2017 in Kuala Lumpur, Malaysia, and attended by >500 delegates from >50 countries, and again questions were invited by completion of forms in hard copy on the day or by online survey. A further 28 questions from 9 people were submitted by hard copy, and 170 questions online from 32 people, following this exercise and an additional request at the LiHRA annual meeting in 2017. Finally, 36 questions were added from oral presentations at the WAAVP conference, having been identified by presenters as of pressing concern in their area of research. In total, 385 questions were submitted from at least 58 people (excluding secondary sources and conference presenters). Participants were based in at least 19 different countries, widely distributed across Europe, and also including Malaysia, South Africa, Pakistan, the USA, Canada, and New Zealand. Elicitation through more specific organisations and interest groups was avoided in case of bias; for example, soliciting questions through the EU COST Action COMBAR, which focuses on combatting anthelmintic resistance in Europe, might have preferentially raised questions on this issue.

The master list was reduced to 100 questions by online vote. Those who submitted questions, and the wider LiHRA membership, were asked to award each question zero, one, two, or three stars, with more stars awarded to questions considered of high general importance and well suited to guide a focused and feasible research project or programme. The objective was to identify questions in important areas that are novel and testable, rather than those that are open-ended, general, or already known. This choice was made using personal judgement, and there was no limit to the total number of stars that could be awarded by each voter. Question order was randomized for each participant. In total, 38 people voted, from a similar geographic profile as that of question submitters, comprising 15 countries, of which 11 were in Europe, with many claiming direct experience of work in a wider range of locations spanning five continents.

Questions were ranked according to total number of stars awarded, and, in case of ties, were separated based on the number of three-star scores awarded. When questions were repeated, effectively making the same point in a slightly different way, the highest scoring version was accepted, sometimes with minor changes to wording, others removed, and the next question on the list promoted into the top 100.

A core group was constituted, including expertise across the subject areas raised, and from outside Europe. The core group made minor edits to questions, and then reached a consensus through written discussion on the split into ten topic areas, which represented major themes in the submitted list. The final list was presented in these subsections, with ranks removed.

The methodology was adapted from earlier exercises in other subjects [10], modified to achieve greater global reach and less modification through repeated rounds of discussion. In this way, it was hoped that the final question list would capture a broad range of questions, unfiltered by expert opinion, relative to synthetic reviews. In the event, there was very little engagement from some parts of the world (e.g., Australia, South America) in spite of efforts to reach those regions, and there was a European bias in the core group, and arguably therefore in the outcome, with a strong focus on anthelmintic resistance. The bias to Europe might be symptomatic of greater relevant research activity here than on other continents. We exhort researchers in low- and middle-income countries in particular to seize the initiative in driving forward the research agenda to meet the needs in their countries, using researchers established elsewhere to support their efforts but not necessarily to determine the questions addressed or approaches used. It is also recommended that future elicitation exercises with similar aims make creative attempts to engage those who are less disposed to contribute, and further lessen the role of authors, for example, by reducing the size and participation of the core group.

rounds of voting and organization followed, and here we list the questions judged most meritorious by a broad panel of specialists. The ten subsections are based on the questions received and were not decided beforehand, and text commentary follows rather than precedes each series of questions, in keeping with the 'bottom-up' spirit of the exercise. The sections are structured to progress in a general direction from processes of infection, through impacts, to control through chemical and alternative means, and include challenges across the spectrum of

### Glossary

#### Animal Task Force (ATF)Appendix A<sup>vi</sup>:

a European public-private platform that fosters knowledge development and innovation for a sustainable and competitive livestock sector in Europe (Box 1).

**Anthelmintic:** a chemical which can be used to control worm infections. Six different broad-spectrum classes are currently widely available for use in sheep (benzimidazoles, imidazothiazoles, tetrahydropyrimidines, macrocyclic lactones, amino acetoneitrile derivatives, and spiroindoles) and four for cattle (benzimidazoles, imidazothiazoles, tetrahydropyrimidines, and macrocyclic lactones). The terms drug, wormer, and de-wormer are commonly used synonyms.

**Anthelmintic resistance (AR):** the heritable reduction in the sensitivity of helminths to anthelmintics when animals have been administered the correct dose of the drug, in the correct manner, using drugs that are within date and have been stored correctly.

**Bioactive forages:** crops or feedstuffs that reduce the numbers of worms in, or available to, a host. The effect can be either direct (anthelmintic activity; reduced survivability of free-living stages on pasture) or indirect (improved nutrition).

**Biological control:** the control of infection using other organisms or their natural products, such as nematophagous fungi (*Duddingtonia flagrans*) or crystal (CRY) and cytolytic (CYT) proteins of the soil-borne bacterium *Bacillus thuringiensis*.

**DISCONTOLAppendix A<sup>vii</sup>:** a publicly funded, open-access database to assist public and private funders of animal-health research and researchers in identifying research gaps and planning future research.

**Faecal egg count reduction test (FECRT):** a commonly used *in vivo* test to assess the efficacy of an anthelmintic through examination of egg counts of groups of animals preadministration and postadministration of an anthelmintic. The reduction in faecal egg counts of treated animals is expressed as

fundamental and applied research. While we make no claim to this list being definitive or complete, it is a snapshot of what researchers in livestock helminthology consider to be important and topical at this time, and we hope that it will stimulate discussion, and renew energy in existing or novel directions.

## Section I. Helminth Biology and Epidemiology

### Hypobiosis

1. What determines emergence of arrested helminth stages in the host, for example, termination of **hypobiosis** in gastrointestinal nematodes in ruminants or cyathostomins in horses, or the end of the mucosal phase of ascarids in poultry?

Hypobiosis is important for perpetuation of helminth populations during adverse environmental conditions. While factors inducing hypobiosis are well described (e.g., cold or dry seasonal cues, or immunity), factors governing the period of inhibition and timing of emergence are poorly understood. Intrinsic parasite factors, host physiology, or seasonality may all play a role [11,12], but the biochemical basis for these is mostly unknown. New molecular methods, for example, transcriptomics, may be useful to understand the mechanisms of emergence from arrest [13]. Resulting knowledge may pave the way for new control options during a phase when the therapeutic arsenal is typically limited due to the very low metabolic activity of the hypobiotic stages.

### Fecundity

2. What regulates egg production in female helminths, and can it be suppressed sufficiently to provide an epidemiological advantage?

3. Will breeding for host resistance (low faecal egg counts) drive nematode adaptation towards increased fecundity to compensate?

Interference with female worm fecundity could contribute to helminth control, and would benefit from detailed mapping of influencing factors, like host dietary, physiological, and immunological status, location in the host, and intrinsic parasite factors, for example, genetic predisposition and environment-induced changes. For example, in *Haemonchus contortus*, worm size is highly correlated with the number of eggs present in adult females, and egg production is limited by host immune regulation [14]. The ability to target fecundity specifically, and the evolutionary responses of parasites to such a strategy, are therefore likely to be highly dependent on other parasite traits as well as host factors.

### Parasite Adaptation to New Hosts

4. To what extent is there an exchange of parasites between wild and domestic ruminants?

5. Does cross-grazing of cattle and small ruminants encourage gastrointestinal nematode species to adapt and cross between hosts?

Gastrointestinal nematode (GIN) species tend to have a preferred host, but there is considerable evidence to indicate transmission and adaptation between livestock species (sheep/goat/cattle) and between livestock and wildlife when either cograzed or grazed alternately on the same pasture [15]. In farming systems, control by means of alternate grazing with different host species has been reported to break down due to parasite adaptation [16]. Older studies often lack genotyping, and apparent infection across multiple host species may therefore constitute different parasite subpopulations or even species with cryptic host preferences, as with

either a percentage reduction as compared to untreated control animals or using the treated animal as its own control (by comparing with the day-of-treatment count).

**FAMACHA:** FAffa MAllan CHArt, a colour-guide chart used to assess the degree of anaemia in an animal via the colour of their ocular membranes to determine the need for anthelmintic administration. Developed by three South African researchers (Drs Faffa Malan, Gareth Bath, and Jan van Wyk) and named after one of the inventors.

**Host resilience:** the ability of a host to perform under parasite challenge.

**Host resistance:** the ability of a host to control helminth infection, for example, as illustrated by low worm burden or low faecal worm egg counts.

**Hypobiosis:** cessation in development of parasitic stages of roundworms within the host under unfavourable conditions, prior to resumption of development when conditions improve.

**Integrated parasite management (IPM):** the use of a combination of multiple control methods (chemotherapeutic and alternatives) to sustainably control helminth infections.

**Livestock Helminth Research Alliance (LIHRA) Appendix A<sup>vii</sup>:** a consortium of researchers that aims to develop sustainable effective helminth control strategies and promote their implementation by the livestock industry (Box 1).

**Plant secondary metabolites (PSMs):** plant products that are not directly involved in normal growth, development, or reproduction, but instead are thought to be waste or stress products or defence mechanisms against herbivores and insects.

**Refugia:** parasite subpopulations from either the stages within the host or free-living stages that are not exposed to anthelmintic treatment, and that have the ability to complete their life cycle and pass on susceptible alleles to the next parasitic generation. This is generally achieved by ensuring that a proportion of the parasite population remains unexposed to drug, through either **targeted treatment** or

lungworms in deer [17]. Whether the impact of cross-transmission between wildlife and livestock is likely to amplify or reduce pasture infectivity, and thus transmission to livestock, is in general an open question and likely to be context-specific [18]. Untreated wildlife could, moreover, act as a source of **refugia** for drug-susceptible genotypes, or alternatively transfer resistant parasites to new hosts or locations [19]. The net effect of livestock–wildlife contact on helminth ecology and evolution is hard to predict.

#### Effects of Climate Change on Epidemiology

6. How do parasitic worms respond to climatic change, and what is their environmental plasticity?
7. What is the effect of climate and weather, especially drought, on the spatial distribution of infective helminth larvae on pasture and on the subsequent risk for grazing animals?
8. How is climate change affecting overwintering of nematodes in temperate areas?
9. Will climate change result in a change of helminth species in temperate environments, or will the existing ones simply adapt?
10. Is the recent increase in the prevalence of rumen fluke in Europe a threat to livestock farming?

Climate changes may not only affect helminths directly (e.g., the external stages and induction of hypobiosis) but also via effects on availability of definitive or intermediate hosts or on habitats, and through land use in agriculture. In general, parasites tend to adapt to the changes happening around them by evolving. Adaptation may involve strain variation in phenology, within-genotype variation in key life history traits, and host switching [20]. Parasites may spread their chances of infecting hosts across variable or changing environments. An example in livestock is the adaptive epidemiology of *Nematodirus battus*, previously having a single generation per year (spring infection), but more recently evolving a strategy of two generations per year, which is better suited to unpredictable spring weather [21]. Parallel work on microbes indicates that sensitivity to environmental variation is itself a trait that can evolve, conferring resilience to changing climates [22]. There is considerable scope to improve predictions and measurements of helminth responses to climate change, in terms of evolutionary as well as epidemiological dynamics, and to include helminths with indirect life cycles such as trematodes, in which adaptive changes in intermediate hosts might also be important. Differentiating climate change from other forces, and proving its role in parasite range expansion, is not straightforward, either for apparently emerging parasites such as the rumen fluke *Calicophoron daubneyi* [23] or for other helminths, and this undermines attempts to predict future challenges to farming. Given the multiple interacting factors that drive parasite epidemiology, research should embed parasitic disease in wider studies of climate change mitigation and adaptation in livestock and mixed agricultural systems [24].

#### Improved Diagnostics for Epidemiological Monitoring

11. Can we develop good ways to enumerate infective helminth stages on pasture?

Various methods have been extensively documented to recover infective stages of GINs and flukes from herbage or tracer animals, followed by microscopic counting and identification by morphological or molecular methods [25]. However, modern quantitative and qualitative molecular methods have not been sufficiently adapted for rapid estimation of the

**targeted selective treatment** (see below).

**STAR-IDAZ:** International Research Consortium on animal health<sup>Y</sup>, comprising research funders and programme owners from Europe, Asia, Australasia, the Americas, Africa, and the Middle East, as well as international organisations, and including representation from veterinary pharmaceutical companies. Members coordinate their research programmes to address agreed research needs, share results, and together seek new and improved animal-health strategies for at least 30 priority diseases, infections or issues (Box 1).

**Targeted selective treatment:** the treatment of only some individual animals within a group at one time, instead of the more common whole-group treatment, where all animals in the group are treated simultaneously.

**Targeted treatment:** treatment of animals at a time selected to either minimise the impact on the selection for anthelmintic resistance, or to maximise animal productivity.

**Zoonoses:** infections that can be transferred from animals to humans.



level of parasite challenge. Success would have clear applications to parasite management as well as improving the feasibility of field studies to test epidemiological and evolutionary predictions.

## Section II. Economic and Environmental Impacts

12. What is the true financial cost of helminth infection?
13. Is profitable livestock husbandry possible without chemical parasite control?
14. Does the control of helminths reduce net methane emission over the lifetime of a ruminant?
15. How can environmental impacts of anthelmintics be properly measured, including on nontarget fauna, and ecosystem functioning and service provision?
16. What are the costs (financial, human, and to animal welfare) of anthelmintic resistance?

### Holistic Economic Estimates of Helminth Impacts

The established aim of helminth control is to reduce parasite burden to improve animal health and productivity. As a result, research has tended to focus on how novel parasite control approaches can achieve higher efficacy and optimise production. Today, increasing emphasis is being placed on the sustainability of livestock farming. Therefore, the use of all inputs needs to be accounted for in the production equation, and the role of helminth infection needs to be clarified in terms of optimal farm resource allocation, as well as its environmental and economic impacts [26]. There is early evidence from experimental and field studies of the beneficial impacts of effective helminth control on reducing greenhouse gas emission intensity in grazing livestock [27–29]. The impact of helminth parasitism on water use efficiency also needs to be better understood. There is a need to extend these approaches to emerging and resurgent parasite species such as rumen fluke and to investigate the direct impacts of failure of control, for example, as a result of anthelmintic resistance.

### Costing Environmental Impacts of Drugs and Drug Resistance

Side-effects of anthelmintics as a consequence of 'leakage' into the environment, such as on nontarget fauna [30], and onward impacts on their ecology and ecosystem service provision [31] need to be better understood and balanced against the beneficial impacts of treatment. The direct costs of anthelmintic resistance include the cost of the ineffective drug, the labour wastage in administering the ineffective drug, and the failure of adequate control leading to reduced production of meat and milk on a per hectare and per animal basis. However, there likely are many other indirect economic and environmental impacts since more animals will be needed to produce the same amount of food [32]. Generating these insights and integrating them into economic frameworks has great potential to support sustainable helminth control programmes at farm, regional, and national levels. Valuing sustainability, and the economic benefits of helminth control in less monetised farming systems, remain challenging [33].

## Section III. Effects on Host Behaviour and Welfare

17. How can we measure the impact of helminth infections on livestock welfare?
18. How does parasitism affect animal behaviour?
19. Can we use changes in behaviour to identify those individuals that need treatment?

20. Can we select for host behaviour to control helminths?
21. Do ruminants self-medicate by selectively grazing plants with anthelmintic compounds?
22. Are animals better off and healthier with some worms, rather than none? Studies are biased towards negative effects on hosts, and neglect potentially positive outcomes at individual and population levels.

#### Measuring Behavioural Impacts of Parasitism

Research into the impacts of helminth infections on the behaviour and welfare of livestock has largely focused on aspects of direct economic importance in ruminant livestock [34], and is lagging behind research into the behavioural and welfare impacts of parasites in other host–parasite systems [35]. The impact of subclinical helminth infection on host behaviour and welfare indicators remains largely understudied, perhaps in part because such subclinical effects can be hard to detect and difficult to separate from those of other disorders. Still, changes can be more objectively measured today using new technologies. Thus, advances in electronic technology (e.g., 3D accelerometers) offer novel tools to monitor and detect host welfare and behavioural responses to parasitism and to link these to targeted control efforts [36]. Further, positive behaviours that allow livestock to avoid or suppress infection, such as self-medication and selective grazing, may be identified as markers to selectively breed for ‘behavioural’ resistance [37]. The importance of behaviour as a defence strategy against GINs is recognized in goats [38], but empirical evidence for selectively breeding grazing animals to develop this trait is so far lacking.

#### Helminth Infection Is Not Necessarily Negative

Studies to date focus on negative effects on hosts and neglect potentially positive outcomes of helminth infections, such as regulatory roles at scales ranging from gut microbiomes and inflammation [39] to entire grazing systems [40]. Studies taking a more holistic view of the consequences of infection for individual and group health would be timely given changes in farming systems and increasing societal concern in many countries for the welfare and environmental costs of modern farming practices.

### Section IV. Host–Helminth–Microbiome Interactions

23. How do gastrointestinal parasites communicate in the gut?
24. How does interaction between different helminths in coinfection affect the immune system of the host and the development of disease?
25. Are there associations between animals’ microbiomes and helminth communities, and do they matter?
26. Can the alteration of gut microbiota influence immunity to parasites in livestock, and vice versa?
27. To what extent do coinfections between helminths and other specific pathogens – for example, liver fluke and bovine tuberculosis; gastrointestinal nematodes and paratuberculosis; lungworms and respiratory pathogens – influence health outcomes for livestock and human health?

#### Helminths Interact with Other Infections, but Consequences Vary

The ability of helminths to influence the host response and dictate disease outcomes of coinfections is an active area of research within parasitology [41] in which many questions remain unanswered. In

classical coinfection scenarios, a coevolutionary dynamic between the vertebrate host, helminths, and microbiome is thought to result from complex adaptations of each of the three components [42]. Research into helminth-microbiota coinfections in livestock hosts is in its early stages, raising questions about whether a host's microbiome and helminth community interact and communicate, how any such interaction impacts on the host immune response to both natural infections and vaccines, and whether it can be manipulated to enhance host immunity. Inconsistencies exist between different studies, methodologies, and approaches, but a growing body of evidence from humans and rodent model systems has identified helminth-associated changes in gut microbiota [43,44]. It remains to be established whether this occurs as a direct effect of the parasite itself or as a secondary effect driven by the host and its immune response, or perhaps both [44]. Clearly, a better understanding of coinfections (in consideration also of different helminths, or of helminths and microorganisms), the mechanisms they invoke, and, importantly, their impact on the health and productivity of livestock is required [45,46]. A systems biology approach, drawing insights from diverse host environments (e.g., including livestock and wildlife systems), pathogen combinations, and stages of infection [41,44,47–49] offers promise to advance our knowledge and identify potential alternative strategies for parasite control. A truly holistic view would also include the impact that helminths and their control may have on other diseases and their detection, including **zoonoses** [50].

### Section V. Host Resistance, Resilience, and Selective Breeding

28. Have 60 years of intense anthelmintic use changed the relative susceptibility of livestock to parasites? In other words, are animals less robust than they used to be as a result of protection from the effects of parasites by drugs, thereby causing selection of higher-producing but more parasite-susceptible animals?

29. How can **host resilience** and **host resistance** of ruminants to helminths be measured and distinguished?

30. Is resistance, tolerance, or resilience the best breeding objective to produce livestock that require less anthelmintic treatment? Under what circumstances should breeders aim for each?

31. Breeding for resilience (high production potential in spite of elevated faecal worm egg counts) could result in significantly increased pasture contamination over many years. What will the impact of higher challenges be on resilient individuals? Will the resilience break down above a certain threshold?

32. Can **targeted selective treatment**, for example, using **FAMACHA**, be used to select for parasite resilience, especially among low-input traditional breeds?

33. In nonselective breeding systems, does targeted selective anthelmintic treatment support weak animals and lead to loss of resilience at herd or flock level?

34. What are the life-time trade-offs between immunity to helminths (resistance) and impacts on growth and production (resilience) in different livestock systems?

35. Which are the main differences between cattle, sheep, and goats in terms of resistance or resilience to helminth infection?

36. Which genotypes of livestock hold natural resistance to helminths, and how can they be exploited in modern production systems?

37. Why are some animals more prone to heavy parasite burdens than others?



### Selecting Optimal Host Phenotypes Is Not Straightforward

Variation in susceptibility to parasites is multifactorial. Differences clearly exist between host species, and these differences seem to derive from the evolutionary forces in play with regard to grazing behaviours and the climate and environment where different hosts evolved. However, even within host species, genetics, faecal avoidance behaviour, and immunological differences exist [51,52]. Moreover, the timing of measurement is important in distinguishing between resistant and resilient animals as, should immunity develop, animals may thereafter display a mixture of both resistance and resilience. Resistance is undoubtedly favourable when faced with a fecund or highly pathogenic parasite, such as *H. contortus* [53]. In contrast, resilience is associated with larger body weights and greater growth in the face of helminth challenge, and can be reliably assessed based on the number of treatments required using a targeted selective treatment regime [54,55]. Resilience, when it involves greater tolerance of infection, generally results in greater pasture contamination, but resilient animals also by definition have a greater threshold of parasite challenge before incurring loss of productivity [52]. Whether the long-term epidemiological benefits of resistance outweigh the missed growth opportunities remains to be determined, although the risk of pasture contamination becoming too great if resilience is selected will depend on the environment and grazing management, both of which influence transmission within and between seasons. There are undoubtedly physiological costs to resistance, and the interplay of resistance versus resilience (or tolerance) may differ between different parasite species depending on their pathogenicity. These distinctions are important because hosts that are best at controlling parasite burdens are not necessarily the healthiest, but can have a positive impact on the herd infection levels by decreasing pasture contamination. Ultimately, resistance and resilience/tolerance will have different effects not only on the epidemiology of infectious diseases, but also on host–parasite coevolution [56]. The pursuit of improved host responses to parasitism through selective breeding therefore requires optimization across multiple dimensions, including characteristics of the main parasites of concern now and in future, production aims and farm management system, and should guard against unintended consequences for coinfections.

### Section VI. Development and Detection of Anthelmintic Resistance

38. What is the relative importance of management versus environmental factors in determining the development of anthelmintic resistance in livestock?

39. How does animal movement affect the spread of helminth infections and anthelmintic resistance?

40. What changes in genes other than those encoding the immediate drug target, such as transporters and drug metabolism, are involved in anthelmintic resistance?

41. What do we understand about the fitness costs of anthelmintic resistance, and how can they be measured?

42. Has selection for drug resistance changed the pathogenicity of parasites?

43. Is there a link between the size of the refugia needed to slow or prevent anthelmintic resistance and the molecule and formulation used (e.g., persistent versus nonpersistent)?

44. Can combination anthelmintic formulations be designed that are more effective and that limit resistance development?

45. Do differences in life-history traits and reproductive strategy affect the risk for development of anthelmintic resistance?
46. What is the effect of long-lasting drug formulations, such as moxidectin injections or benzimidazole boluses, on the development of anthelmintic resistance in sheep, goats, and cattle?
47. Is treatment of ectoparasites with macrocyclic lactone drugs an important driver of anthelmintic resistance in sheep and goats?
48. Are *in vitro*/genetic/laboratory methods for detection of anthelmintic resistance desirable, reachable, and applicable for all anthelmintic drug groups?
49. How can we best improve monitoring of the efficacy of current control methods (e.g., through diagnostics, resistance testing, and surveillance)?
50. How useful are composite faecal egg counts to detect anthelmintic resistance?
51. What is the true status of anthelmintic resistance in less-studied livestock systems, for example, ascarids in pigs and poultry?
52. Is there compelling genetic evidence for reversion to drug susceptibility under any circumstances?
53. How can the prevalence of anthelmintic resistance be practically measured in a way that minimises bias?

#### Mechanisms and Processes in Resistance

The evolution of AR in parasitic helminths is considered to be driven by a range of parasite intrinsic and extrinsic factors [57]. To the former belong drug- and species-specific susceptibility, effective parasite population size, and genetic variability. External factors include treatment frequency and intensity, and the size of the refugia, which strongly depend on local management and environmental determinants. How these factors interact and influence the development of a phenotypically resistant worm population is currently largely unclear. Also, the molecular mechanisms of AR are not well established for most combinations of helminth species and drug groups. Nevertheless, in the case of the benzimidazoles, a well developed understanding of the resistance mechanism has enabled molecular tools to be established for AR detection, which can be used to elucidate patterns of spread of resistance on a broad scale for ruminants [58]. The situation in pigs and poultry, however, is barely known [59].

#### Towards Better Diagnosis of Anthelmintic Resistance

There is a great need to extend our knowledge of the driving forces of AR development, to establish field-applicable and meaningful resistance-detection tools, and hence to provide more up-to-date and reliable information on the occurrence of AR. In an era of revolution of technology in the diagnostic industries, improvement of the 'old-fashioned' **faecal egg count reduction test (FECRT)**, for example, through the use of pooled faecal samples [60–62], or eventually automation, has great potential to allow more rapid, labour-efficient, and remote assessment of AR. This remains a worthwhile aim because definitive molecular tests remain elusive for most drug groups and helminth species. Better tests would enable AR to be distinguished from other causes of poor efficacy, including through the administration of

substandard generic compounds [63]. Links between AR in livestock and humans, through zoonotic transmission of resistant parasites such as *Ascaris* spp., and in terms of potential for shared understanding of mechanisms and approaches to limit AR, remain underexplored.

## Section VII. Practical Management of Anthelmintic Resistance

### When to Intervene against Resistance

54. What is the usefulness of anthelmintics working at decreased (e.g., 50% or 80%) efficacy?

55. When should drug combinations be used to combat anthelmintic resistance, and when not?

Optimal usage of anthelmintic drugs in the face of AR should be tailor-made and consider parasite species, host species, farm management, and climatic factors [2,3]. Deciding how to extend the lifetime of drugs, either before or after some resistance is evident [64,65], requires consideration of actual levels of AR and how fast AR spreads given selection pressures imposed by factors such as drug type and number of treatments, whether treatments are targeted or not, and the presence of refugia [66,67].

### Refugia in Principle and Practice

56. What empirical evidence is there that refugia slow down the development of drug resistance?

57. What proportion of a helminth population must be left in refugia in order to slow the development of anthelmintic resistance?

58. How does the level of refugia influence the detection and spread of resistant phenotypes in different hosts, different parasites, and different treatment systems?

59. Is there a role for refugia in the control of liver fluke?

60. If refugia are not appropriate for all parasite species that display drug resistance, what realistic alternatives exist for those situations?

61. Can anthelmintic resistance be practically reversed, for example, through targeted selective treatment, good grazing management, or reseeded (community replacement or dilution) approaches?

The concept of refugia is widely accepted, but is still surrounded by several assumptions and approximations, and the level of refugia required may depend on prevailing (e.g., climatic) circumstances [68]. Refugia as a concept has been mainly applied to GINs, but its role in resistance management in other helminths needs further research. Also, the extent to which refugia might play a role in the reversal of AR [65], as opposed to just slowing its development [69], is currently far from clear, as is the practical usefulness of community replacement strategies for regaining anthelmintic susceptibility on farms [70].

### What to Do about Known Resistance Status?

62. What is the value of faecal egg count monitoring as a decision tool for anthelmintic treatments?

63. We are on the cusp of having molecular markers for drug resistance, for example, for macrocyclic lactones in *H. contortus* and triclabendazole in liver fluke. How should we best apply them?

It has become common practice to apply blanket, whole-herd treatments without prior knowledge about infection levels or drug efficacy. To optimize drug usage, such prior knowledge appears to be requisite, and more science is required to create and evaluate new and more practical ways to measure levels of infection and AR.

#### Targeting Treatments against Helminths

64. Is targeted selective treatment sustainable in the long term, or will it decrease parasite overdispersion and hence ability to identify heavily infected individuals?

65. What are the most useful decision parameters in targeting anthelmintic treatments?

66. Is targeted selective treatment a feasible approach with which to control helminths with a very high biotic potential, for example, the ascarids?

Animals within populations show different levels of susceptibility to infection both in terms of resilience and resistance, and parasites are typically overdispersed within host groups. This opens up the path to employ targeted selective treatments of individual hosts, and in the process create and maintain refugia [6,69]. Treatment decision parameters need to be explored more fully; their applicability may depend on parasite species as well as on host production system, and much more empirical work is needed for optimisation.

#### Reaching and Influencing Stakeholders to Optimize Helminth Control

67. Can we automate interpretation of data collected during targeted selective treatment, for farmer decision support and also training?

68. How do we apply existing knowledge of the risk factors for anthelmintic resistance on farms to effectively slow its development?

69. What are the characteristics of an optimal quarantine drench as a way of reducing the risk of importing resistance with bought-in animals?

70. How do we implement better dosing procedures of anthelmintics in cattle in order to ensure therapeutic drug levels (pour-on versus injection/oral)?

71. What practical steps should be taken on a farm when resistance to all known anthelmintic drug classes develops?

Finally, although managing resistance through more effective targeting of treatment is an intuitive approach that is becoming established best practice [6], challenges remain in terms of fundamental understanding of the biological processes involved in AR. Furthermore, how existing knowledge should best be integrated and structured for on-farm application, and communicated effectively through farmer and expert advisory groups<sup>i-iii</sup>, itself needs a more solid evidence base [9]. Effective uptake of alternative helminth management approaches could not only delay AR, but also afford farmers more options if and when AR becomes fixed, for example, following efforts to dilute resistance alleles by introducing susceptible worms [70].

#### Section VIII. Vaccines and Immunology

72. Can the natural immune response to helminths be enhanced by applying a biological treatment (e.g., specific cytokine or cytokine inhibitor) and thereby control infections?

73. Do worms have a microbiome? Can it be exploited as a vaccine or treatment target?
74. How can vaccines against helminth infections in ruminants be integrated in control programmes?
75. In what ways do helminths resist or escape from the host immune system?
76. How well do antihelminth vaccines have to work to be useful?
77. To what extent is the immunomodulation by helminth parasites detrimental to the animal's health when coinfections co-occur?
78. What mechanisms are involved in protective immunity against helminths?
79. What is the potential for a multivalent vaccine to control multiple species?
80. How are optimal helminth vaccination schedules influenced by infection pressure, and can this be incorporated into decision making?
81. How fast do parasites adapt to increased immune selection pressures (for instance due to vaccines)?

#### More Insight Needed into Natural Immune Responses

Helminths typically induce a T-helper 2-type immune response, but the effector mechanisms have not yet been elucidated, and it is not always clear whether this immune response is host protective or to the advantage of the parasite, which is acknowledged as a major knowledge gap [8]. Incomplete knowledge about protective immune responses against helminths hampers vaccine development. Insight into the immune mechanisms would allow informed decisions about adjuvants and antigen delivery [71] and could lead to alternative immune therapies, for example, cytokines or cytokine inhibitors, which has shown potential in porcine neurocysticercosis [72].

#### Integrating Vaccines into Control Programmes

To be useful alternatives to anthelmintics, vaccines should protect against multiple helminth species [71]. At present, there is only one vaccine for gastrointestinal nematodes available; targeting *H. contortus* ([www.barbervax.com.au/](http://www.barbervax.com.au/)) and other experimental vaccines is also limited to single species, and there is no evidence for cross-protection, for example, between *Cooperia* and *Ostertagia* in cattle [73]. 'Multivalent' vaccines could also include those containing multiple antigens of a single parasite species, to avoid or slow down adaptation of the parasites to the vaccine, for example, an experimental *Teladorsagia* vaccine in sheep that comprises multiple recombinant proteins [71]. To protect young animals until natural immunity has developed, vaccines should lower pasture infection levels by reducing worm egg output in vaccinated animals for a useful period [74]. The level and duration of protection needed will be different for different parasites and in different epidemiological settings, for example, on pastures with high or low infection pressure, and may differ with changing climate or farm management.

Vaccination, even if only partially effective, could become an important component of integrated worm-control programmes, including pasture management and anthelmintic treatment [1]. The huge number of possible scenarios could be investigated using helminth transmission models [75–79]. After field validation, these models could ultimately lead to decision support

software for integrated worm control [9]. The sustainability of vaccines, like anthelmintics, will depend on parasite evolution, and the ability of helminths to develop resistance to vaccine-induced host responses remains an open question.

### Section IX. Alternative Approaches to Helminth Management

#### Plant-based Control

82. Many studies have shown a maximum efficacy of bioactive plant compounds around 60–70% reduction in gastrointestinal nematode burden: how can efficacy be driven higher? Is it needed?

83. Can different bioactive plants be combined to increase effects on gastrointestinal nematodes?

84. Can plants be cultivated for grazing that have maximum nutritive value and the potential to lower helminth burden?

85. How does processing and conservation of bioactive forages affect their efficacy?

86. What are the interactions between bioactive forages and synthetic anthelmintic drugs, *in vitro* and *in vivo*?

87. What are the mechanisms of action of bioactive plant compounds and metabolites in relation to parasite establishment and adult worm viability and fecundity?

88. What is the efficacy of plant-based anthelmintics against drug-resistant helminths?

With the increasing emergence of AR in helminths of livestock, alternative options are in demand, especially for the integrated control of GINs. Plants and **plant secondary metabolites (PSMs)** appear to be a promising option. Different PSMs (e.g., tannins) have shown antiparasitic effects when used as nutraceuticals [80] or in phytotherapy [81]. Two hypotheses have been invoked to explain the anthelmintic properties of PSMs [82]: pharmacological-like effects through disturbance of the parasite life cycle [83], or indirect effects on the host immune response [84]. In both cases, more studies are needed to identify the mechanisms of action of PSMs and their effect on helminth populations, including those with high levels of AR, as well as the potential role of PSMs in managing helminths other than GINs. Feeding 'bioactive forages' can also improve nutrition and performance, and reduce GHG emissions, quite apart from any impacts on helminths.

The interactions between different PSMs and between PSMs and anthelmintics remain largely unexplored, and contrasting results have been described [85]. The development of refined methods to assess the anthelmintic potential of plant compounds is needed. Some practicalities around the use of PSMs on farms also need to be addressed, such as regulation of mode of distribution, level of inclusion in feed, and potential residues in animal products.

#### Other Alternative Control Methods

89. What are the main obstacles (not only technical) to the development of new technologies to control helminths of livestock?

90. Can we target helminth stages outside the host to achieve control, for example, killing stages on pasture or manipulating intermediate host biology?



91. Are there basic processes in egg hatching or larval development that can be manipulated to aid control?

The objective of **integrated parasite management (IPM)** is to limit the level of parasitism below acceptable limits while delaying the emergence of drug resistance. This aim has motivated the search for and refined use of PSMs as well as other alternatives to commercial chemical anthelmintics, including vaccines, host resistance, and grazing management [86]. Good pasture management is one of the major means to limit the intake of infective larvae by animals, for example, by the use of parasite-free fields, pasture rotations, and alternation of grazing animals, taking into account the seasonal dynamics of helminth transmission. Manipulation of environmental conditions that play a role in the development of intermediate stages may also be a form of alternative control. For example, grazing away from wet pasture, where feasible, markedly lowers the risk of *Fasciola hepatica* infection, due to lower exposure to infection near intermediate snail host habitats [87]. Free-living stages of GINs may also be targeted directly, for instance through application of urea or other nitrogen-based fertilisers to pasture [88,89]. Certain bioactive forages, for example, chicory, are also thought to hamper the development of free-living stages, either by reducing the fitness of eggs excreted from hosts grazing on the forage, or because the physicochemical properties of the forage reduce larval availability on herbage [90]. Biological control based on nematode-trapping fungi (*Duddingtonia flagrans*, *Arthrobotrys musiformis*) or entomopathogenic bacteria can also reduce the number of free-living stages on pasture and the level of host infections; results from mechanical stressors, such as a diatomaceous earth, are less promising [91,92]. Refined understanding of the mechanisms of action of these nonchemotherapeutic alternative control methods, and how they might be applied to manage helminth populations on farms, provides potentially fruitful avenues for further research.

## Section X. Stakeholder Engagement

### New Decision Support Tools for Helminth Control

92. How can different novel control methods for helminths be integrated effectively and in a way that is simple enough for farmers to implement?

93. Can helminth-control-decision-support tools be integrated effectively in farm or pasture management software?

94. How can we transfer automated technology to farmers, especially those who are resource-poor?

95. Is research in veterinary helminth infections reaching livestock farmers in developing countries and, if so, what is the impact?

Veterinary parasitologists working with livestock might consider extending their efforts from task-oriented research targeting the development and refinement of helminth control strategies, and advance towards advice-oriented health-management practices. To achieve this would involve answering some key research questions around development of decision-support tools that can integrate different worm-control strategies into whole-farm management [9], taking into account also the regulatory frameworks and economic environments in which farmers operate. Researchers are now looking further down this road and questioning how their strategies will fit best into the whole-farm environment and how decision tools can be integrated, for example, in farm-management practices and decision-support systems. Even

though there is considerable knowledge on available complementary strategies, substantial deficits remain around knowledge exchange and transfer, and the research community is becoming increasingly aware that better promotion of such strategies to the farmers is crucial for their success [93].

#### Understanding Farmer Behaviour to Support Effective Knowledge Exchange

96. What factors drive anthelmintic treatment decisions by farmers?
97. How can the importance of a strategic approach to helminth treatment be more effectively promoted among producers, especially when drug resistance is not yet an issue?
98. What can we learn from social sciences to transfer knowledge on helminth control to farmers?
99. How does the attitude of farmers with respect to accepting and implementing parasite control measures differ between countries and cultures?
100. How will consumers influence livestock-production practices, in terms of anthelmintic use?

In order to develop control methods that are effectively applied, it is necessary to obtain insights into factors that drive farmers' decisions about worm control and use those insights to develop communication strategies to promote sustainable worm-control practices [94]. Major reasons why suggested solutions often do not fit with farmers' views are that they are highly complex (involving language and cultural barriers) and not cost-efficient (too expensive), encompass conflicting interests (e.g., intensive versus extensive farming systems) and priorities, and may require contradictory management interventions at farm level. Consequently, educating and motivating farmers and adopting a multiactor approach are key issues. Stronger empirical evidence for the effectiveness of integrated parasite control strategies and their compatibility with performance targets is key to adoption [94,95]. Researchers must understand the fundamental and instrumental relationships between individual farmers' values, behaviour, and perception of risk, to stimulate and qualify the farmer's decision-making in a way that will increase the farmer's satisfaction and subjective wellbeing, and not only narrow metrics around performance or financial return [26,96].

Factors that influence farmers' behaviour are not limited to technical or practical issues such as ease of use or price, but also include less 'tangible' factors such as the opinion of others or habits [97–99]. Barriers and incentives for sustainable worm control that were identified in such quantitative and qualitative studies may vary between farmer types (e.g., sheep farmers versus dairy-cattle farmers) or between countries. Moreover, before these factors can be translated into communication strategies, they should first be validated in communication experiments [100]. In the literature on changing animal health behaviour, the majority comprises studies that investigate the factors that influence behaviour intention, which at best suggests which social intervention could be developed to change this intended behaviour, but rarely assess whether such intervention could work [101]. Finally, human behaviour (and thus also farmer behaviour) is also strongly influenced by unconscious processes, such as intuition, which has not yet been studied in the context of sustainable parasite control [102].

As a community, veterinary parasitologists need to adopt a transdisciplinary approach, together with epidemiologists, social scientists, economists, and others (including livestock

scientists, grassland-management experts, conservationists, processors, retailers, and farmers themselves), which will result in a better understanding of farmer behaviour and motivation with respect to drug treatments and parasite control.

### Concluding Remarks

The questions listed above were the result of an attempt to elicit research priorities from a wider constituency than in more usual review formats, which are typically led by a small number of established experts. It was anticipated that this would yield a wider-ranging set of potential research topics and directions, less constrained by forces that shape disciplinary academic consensus. In the event, the topics and questions are broadly similar to those raised in recent expert reviews [1,4,6–8,103], and they reflect a high level of current concern over the biology of AR, how to measure and manage it, and the quest for alternative options for the control of helminths on farms. This is perhaps not surprising given that improved helminth management is a key goal of most researchers in the discipline, whether they lean towards fundamental or applied research, and that AR is the main threat to existing control strategies. Control of helminth infections in mainstream farming systems with fewer chemical inputs is a topical challenge and one that will require new research, technologies, and perhaps economic goals [1].

Questions around helminth epidemiology, management of AR, and alternative control approaches including refugia, were frequently repeated in the original list (see the supplemental information online), for example, being posed more than once for different parasite or host taxa. To achieve feasible smaller research projects, as envisaged at the start of this exercise, many of the questions could be broken back down again to specific taxa, both to produce system-specific knowledge and applied solutions, and to explore the generality of conclusions from more studied contexts. Challenges in tropical or less-developed countries yielded few specific questions, as did those related to pig and poultry production. Participation was also strongly skewed towards European countries, in spite of efforts to be inclusive, possibly as a result of the European roots of LiHRA, under whose auspices the exercise was conducted (Box 1). Nevertheless, questions submitted from outside Europe focused on similar topics, and almost all of the final questions are relevant across wide geographic areas and often globally. The voting round (Box 2) might also have distorted results and led to the loss of original, but less popular, ideas from the final list, though such a step was necessary to limit numbers of questions and exclude some to which answers are already well known.

While not definitive, the final list of 100 questions serves to indicate current concerns among the livestock helminth research community, and highlights several areas in which existing understanding is poor while fresh advances now appear possible. The questions might serve to encourage or inspire work in those areas. For example, early-career researchers might peruse the list to identify topics on which short or starter projects might have disproportionately high impact on the state of knowledge. It would be instructive to repeat this exercise in future, to determine how many of the questions have been answered, and whether the state of knowledge, the enabling technologies, or the problems of the day have moved sufficiently to generate different gaps and priorities. In the meantime, as a community, there is clearly work to be done to explore interesting questions whose answers are highly relevant to the ability of humankind to feed itself in the future while respecting the global environment and the health and welfare of the animals that sustain us.

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### Resources

- <sup>i</sup>[www.cattleparasites.org.uk](http://www.cattleparasites.org.uk)
- <sup>ii</sup>[www.scops.org.uk](http://www.scops.org.uk)
- <sup>iii</sup>[www.wormboss.com.au](http://www.wormboss.com.au)
- <sup>iv</sup>[www.discontools.eu](http://www.discontools.eu)
- <sup>v</sup>[www.star-idaz.net](http://www.star-idaz.net)
- <sup>vi</sup>[www.animaltaskforce.eu](http://www.animaltaskforce.eu)
- <sup>vii</sup>[www.lihra.eu](http://www.lihra.eu)
- <sup>viii</sup>[www.legumeplus.eu](http://www.legumeplus.eu)
- <sup>ix</sup>[www.waavp.org](http://www.waavp.org)

### Supplemental Information

Supplemental information associated with this article can be found, in the online version, at <https://doi.org/10.1016/j.pt.2018.10.006>.

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