MEETING SUMMARY

4TH COMBAR JOINT WORKING GROUP MEETINGS

ANTHELMINTIC RESISTANCE IN RUMINANTS: FROM RESEARCH TO RECOMMENDATIONS

FEBRUARY 2021

cost EUROPEAN COOPERATION IN SCIENCE & TECHNOLOGY

COMBAR

Authors of the report
Johan Höglund - Swedish University of Agricultural Sciences, Sweden
Gillian Mitchell, Fiona Kenyon, Philip Skuce – Moredun Research Institute, UK
Johannes Charlier – Kreavet, Belgium

Report coordination, editing and design

KREAVET

Acknowledgement
This publication is based upon work from COST Action COMBAR CA16230, supported by COST (European Cooperation in Science and Technology).
COST (European Cooperation in Science and Technology) is a funding agency for research and innovation networks. Our Actions help connect research initiatives across Europe and enable scientists to grow their ideas by sharing them with their peers. This boosts their research, career and innovation.

www.cost.eu • www.combar-ca.eu

cost
EUROPEAN COOPERATION IN SCIENCE & TECHNOLOGY

TABLE OF CONTENTS

ABOUT COMBAR AND THE VIRTUAL SYMPOSIUM

Cattle, sheep and goats are parasitised by various helminth species. These pathogens are important production-limiting diseases of grazing ruminants in Europe and are mainly controlled through grazing management and the strategic use of anthelmintics. Today, anthelmintic resistance (AR) has become a global threat for effective parasite control and productive livestock farming. The COST Action COMBAR aims at coordinating research at the European level to find solutions for the AR problem. The action works in a structure of 3 working groups: (1) Diagnosis; (2) Socio-economic aspects and (3) Sustainable control.

COMBAR, established in 2017, has grown to a network of near 200 scientists (31 countries) from Europe and beyond, who have been working collaboratively to develop new insights and significant advances in sustainable helminth control in ruminants. After three successful scientific meetings in Warsaw, León and Ghent, where each time over 150 specialists from across the world came together to discuss their work and innovations, in 2020 the meeting was organised in the form of an online symposium, due to the COVID-19 restrictions. This format however, also enabled to reach out to a wider audience including farmer, veterinary and regulatory organisations, and global participants. Indeed, as COMBAR is over half way through, it is time to see where we stand and start defining evidence-based recommendations.

The webinar took place on 9th and 10th December 2020 and was organised in three sessions of two hours each, following the working group structure. In each session, there was a general introduction on the status of the action and activities by the working group leader, followed by an invited presentation, short scientific presentations by COMBAR scientists, and a discussion with invited panel members. The audience participated in the discussion through a polling software.

The webinar was attended by 268 participants from 42 countries (See Appendix 3), with the number of participants per session varying from 157 in session 2 to 186 in session 1. Most participants came from Europe (Figure 1), but there were also participants from Africa, North and South America and Australasia.

Fig 1. Word cloud of the main participating regions / countries in the webinar.

This report aims to summarise the keynote presentations and the outcomes from the discussion panels and audience contributions. Recommendations were distilled from these different contributions for animal disease control and research policy. The recommendations were reviewed by the scientific committee of this meeting. They will be further refined during future COMBAR activities.

The webinar was recorded and **all presentations can be accessed** via the Action's website (www.combar-ca.eu) or directly via the COMBAR YouTube Channel. The abstract book and poster booklet containing results from the scientific presentations are also available via the action's website.

SESSION 1

IMPROVING DIAGNOSIS

The development of low-cost, easy-to-use, multiplex and/or pen-side diagnostic systems for the major helminth infections of ruminants is of high importance to implement diagnostic approaches in helminth control. Currently, most institutions/labs are using their own diagnostic system. Moreover, novel tests are only available in a few well-equipped research institutions (e.g. MT-PCR, LAMP, ddPCR, nemabiome sequencing or bead-based multiplex systems), and mostly not yet in the field. There is a need to compare the performance and cost-effectiveness of the different available diagnostic platforms across countries.

Reliable diagnostics to determine the need for anthelmintic treatment and anthelmintic efficacy are of pivotal importance. COMBAR exchanges knowledge of the available diagnostic tests/platforms across the network and prioritises tests with a broader applicability or industry appeal. It promotes the conduct of market analyses in order to identify opportunities, barriers and challenges that might affect the use of helminth diagnostics in Europe, such as recently carried out for the Mini-FLOTAC technology [1].

The detection of AR has been improved and made more cost-effective by the use of composite faecal samples and the development of DNA-based methods for precise identification of the parasite species surviving anthelmintic treatment. COMBAR is further validating these systems and implementing them to assess the current prevalence of AR in Europe. This resulted in the most comprehensive meta-analysis and database of the status of AR in ruminants in Europe to date [2].

KEY POINTS OF INVITED PRESENTATION BY DR. CÉDRIC NEVEU (INRAE) – MONITORING ANTHELMINTIC RESISTANCE: FROM PHENOTYPIC ASSAYS TO MOLECULAR MARKERS

- Molecular markers for resistance are essential if we are to develop quick and easy tests for AR, predict the occurrence of cross-resistance (one anthelmintic molecule selecting for resistance against another, mostly related, anthelmintic molecule) and monitor the spread of resistance alleles.
- Molecular markers can be identified through (i) a candidate gene strategy (e.g. based on *C. elegans* data), or (ii) a "without a priori approach" where susceptible and resistant worm populations are compared at the genomic or transcriptomic level.
- There is accumulating evidence that cross-resistance does not always occur and that resistance can be reversed, at least for levamisole.
- An Automated Larval Migration Assay (ALMA) based on spectrofluorometric monitoring of the motility of larval stages has been developed. It is suitable to predict anthelmintic efficacy from a wide range of anthelmintic drugs, including macrocyclic lactones and a wide range of parasitic species. The tool can be used to evaluate the robustness of molecular markers and will also be developed as a decision-making tool to inform anthelmintic treatment decisions in the near future.

[1] *A qualitative market analysis applied to mini-FLOTAC and Fill-FLOTAC for diagnosis of helminth infections in ruminants. Frontiers in Veterinary Science (2020) 7, 738.*

[2] *Increasing importance of anthelmintic resistance in European livestock: creation and meta-analysis of an open database. Parasite (2020) 27, 69.*

PANEL DISCUSSION

Chair: Prof. Laura Rinaldi (UNINA)

Panel members: Prof. Georg von Samson-Himmelstjerna (FUB), Dr. Smaro Sotiraki (HAO Demeter), Dr. Menno Holzhauer (Royal GD Deventer), Eurion Thomas (Techion Ltd)

- **There is still a long way to go to increase uptake of FEC or other parasite monitoring tools such as milk ELISA on farms.** The story of AR can be exaggerated and it is important to stress the many other benefits of monitoring parasites: knowledge of your herd, target treatments, responsible use of medicines, performance benefits. Recently, the environmental issue (emissions from livestock) is becoming very important and parasites have an important role to play in this. When promoting diagnosis, the limitations should equally be acknowledged. In the case of FEC methods, these are in particular the fact that only adult parasites are detected, whereas larval stages can also be responsible for disease and the variability between test results.
- **The best use of FEC is by regular monitoring throughout the season**, rather than to use as a one-of-diagnostic. The farmers who use it in the former way are the most satisfied about the results. It allows to build a picture of the farm, share results with veterinary advisor and inform management plan.
- **Prescription of anthelmintics only for high FECs is not a good idea.** FEC is just one of the parameters to inform treatment decisions and you need a broader picture.
- **A farmer expects a fast, reliable and affordable laboratory diagnosis.** Diagnosing parasitic infections should consider the epidemiologic situation of the whole herd. Besides diagnostics for acute problems, mainly seen in young animals, a modern laboratory also has to offer services for sub-clinical infections, which are a common problem for parasitic infections. An excellent back office must be available to be supportive for the interpretation of the laboratory results and the follow-up if necessary.
- **The role of the veterinarian is to advise the herdsman** to monitor the herd for parasitic infections properly, to advise on treatment or not (metaphylactic, preventive, vaccination) and to monitor the effect of the treatment. The challenge for the veterinarian is in the first place to select the animals for examination and treatment, apply the correct therapy, but also to perform expectation management. The epidemiology of parasite infections can be complex and to be able to provide good advice and proper handling of pharmaceuticals, a good knowledge of the epidemiology is essential.
- Despite significant progress in recent years, we are far away from having a universal molecular test to monitor resistance in the field against the different anthelmintic classes. that is applicable in the field. **The great challenge to overcome is the huge genetic versatility of worm species** and the many different molecular mechanisms that make worms resistant to anthelmintics. In the absence of usable molecular tests, in-vitro phenotypic tests such as larval motility assay developed by INRAE and others can be an attractive alternative.
- **The prevalence of AR varies across Europe.** For instance, there are fewer reports from Southern and Eastern Europe. Besides the climate related factors (e.g. cows mostly raised indoors in Southern Europe and no anthelmintics are needed) and husbandry related factors (more small scale farming with treatment seldom applied), there is also the issue of research effort. There has been less attention to and research towards AR in Southern and Eastern Europe, and this explains at least in part the lower apparent prevalence of AR.

PARTICIPANT FEED-BACK

A large majority of the meeting participants (109 respondents over the whole session) perceived that **AR was on the rise in Europe** (Figure 2). The kind of diagnosis to underpin sustainable parasite control was recognised to depend on the host & parasite species and the production system. Many respondents thought that a combination of in vivo and molecular tests would be the ideal diagnostic scenario for underpinning parasite control. While a large majority agreed that **regular FECs and the FECRT** (faecal egg count reduction test) are today the mainstay to monitor nematode infections and anthelmintic efficacy, several were optimistic that **molecular techniques**, which today are still in a research phase, are on the horizon for use in the field. A combination of parasite diagnostics with animal performance metrics was also mentioned to be an important asset to support productive farming. **Diagnostics were thought needed to be quick, inexpensive and user-friendly**. These were also the main criteria identified for diagnostic needs to assess anthelmintic efficacy in the field (Figure 3). Other criteria to this respect included reliable, standardised, penside, portable, repeatable, non-invasive and requiring minimal animal handling.

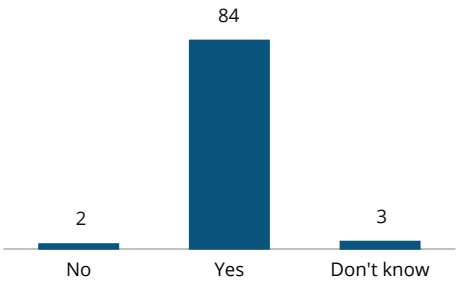


Fig. 2. Results from participant polling if they perceived AR to be on the rise in Europe.

Fig. 3. Participants feedback on diagnostic needs to assess anthelmintic efficacy in the field.

RECOMMENDATIONS

1. Develop multi-actor approaches involving veterinarians, farmers, pharmaceutical industry and research bodies to create awareness and identify solution paths in mitigating the escalating spread of AR.
2. Train the trainers: develop training programmes to empower veterinarians and herd advisors in understanding the complex epidemiology of parasitic helminth infections and delivering evidence-based advice to farmers.
3. Increase research efforts and harmonize investigational approaches on helminth infections and AR in Southern and Eastern European countries, where knowledge of epidemiology, AR and control of helminth infections is poor relative to other European regions.
4. Upsurge implementation of “omics” approaches to unravel molecular mechanisms underpinning AR and lever the development of cost-effective in vitro and molecular tests for AR.

SESSION 2

SOCIO-ECONOMIC ASPECTS

There is a lack of understanding of the economic effects of novel parasite control approaches. Such information is critical before well-founded recommendations can be given. Moreover, in contrast to earlier beliefs, farmer's management decisions are not only based on rational economic considerations, but also depends on intrinsic factors like attitude, risk perception, social norms and trust. Socio-psychological models can help to identify intrinsic motivations on farmers' decision- making processes. Conceptual models that identify all the important factors to predict farmer behaviour can be developed based on theoretical models from human behaviour sciences. COMBAR provided training to researchers on economic and socio-psychological research methods and is applying these to create deeper knowledge of these issues. A European-wide assessment of the economic burden of gastrointestinal nematodes, the common liver fluke and bovine lungworm infections was conducted [3], demonstrating that these infections are responsible for a vast annual burden to the ruminant livestock industries and suggesting there is a large need for improved or better implemented control methods to reduce this burden.
COMBAR is validating a framework based on theories of behavioural psychology and health psychology to gain a deeper understanding of the factors affecting dairy cattle and sheep farmers' intention to adopt diagnostic measures and sustainable worm control measures. The survey is conducted in several European regions and ultimately, this should facilitate the development of control approaches with a high adoption and maintenance by the farmer and targeted communication strategies.

[3] *Initial assessment of the economic burden of major parasitic helminth infections to the ruminant livestock industry in Europe. Preventive Veterinary Medicine 182, 105103*

KEY POINTS OF INVITED PRESENTATION BY DR. MÁRIA SZABÓ (OIE) – OIE'S ACTIVITIES ON ANTIPARASITICS RESISTANCE

- During OIE Focal Point Training Seminars held across Africa, the Americas, Asia and Oceania and Europe in 2017-2018 a deep-rooted need to work on OIE standards and guidelines on prudent and responsible use of antiparasitics became evident. It was concluded that urgent actions, led by the OIE should be considered.
- There are many challenges to overcome including resistance to many antiparasitics (in particular trypanocides and anthelmintics), poor pipeline to deliver novel quality drugs, poor-quality products on the market (substandard or falsified), poor treatment practices, drug residues in the environment and in food and lack of legislation and of appropriate authorisation of veterinary medicinal products in many countries.
- An Electronic Expert Group (EEG) on Antiparasitic Resistance was established in 2019. This group is preparing a document on responsible and prudent use of antiparasitics in food producing animals. The publication of this document is expected in the summer of 2021.
- The EEG on Antiparasitic Resistance has organised a survey in Asia, Africa and the Middle East identifying the lack of diagnosis of resistance as the biggest knowledge gap.
- Based on the surveys, the following conclusions were drawn. There is need for more research and awareness on the topic of antiparasitic resistance. The capacity for diagnosis needs to be grown. The development of standards on the prudent and responsible use of antiparasitics would facilitate progress in these areas. Transnational collaboration is key in addressing the problems associated with antiparasitic resistance.

PANEL DISCUSSION

Chair: Prof. Edwin Claerebout (UGent)

Panel members: Dr. Lesley Stubbings (LSCC Ltd.), Dr. Dave Bartley (Moredun), Dr. Erwin Wauters (ILVO), Dr. Katarina Gustafsson (sheep consultant)

- Awareness of AR is already high in some areas and sectors such as in UK sheep farmers. However, the threat of AR is not enough to induce behavioural change. The problem of AR is that it is an insidious process: you don't see the problem until you have reached the point of no return. So the question is how can we change practices when people still don't perceive there is a problem? Therefore, incentives to induce behavioural change towards sustainable parasite control practices should be based on **a positive "good farming" concept**, rather than being based on beating farmers with the story of AR. This concept takes a wider view on the farm activities and focuses on what makes a farmer feel he/she is doing the right thing. A side-benefit is then the reduced selection for AR.
- **Sustainable parasite control as seen by a farmer** could be described as "producing lambs without resistant worms and with few anthelmintics". It should be good for the economy as well as for the consumer. Sustainable parasite control can be achieved when most farmers agree on the same strategy/priorities. It is based on a combination of good economy and responsibility taking by the whole value chain (from producer to consumer). Use of diagnostics has a clear role in sustainable parasite control and this could greatly be enhanced by a prescription based on diagnosis policy.
- Experience in antibiotic resistance has shown that the most effective way forward is to **establish a critical mass of all relevant stakeholders** (such as SCOPS [4] and COWS [5]) and making these different organisations sit together to decide on concrete targets and deliverables. This is the only way to create sufficient awareness, build capacities and take widespread actions. Countries that have established such stakeholder groups have been the most successful in reducing antibiotic usage. Secondly, data-infrastructures at the national level to collect, monitor and analyse and report antibiotic usage and resistance data have been very important in addressing antibiotic resistance. Such high-level activities have proven to be essential in making changes also at the farm level, and could be transferable to antiparasitic use.
- Production of leaflets and other dissemination materials to create awareness can be very ineffective. **Working one-on-one by coaching, advising, training …** seems much more costly but can be very cost-effective in achieving concrete results. Communication is about building confidence and trust: farmers working with other farmers, veterinarians and advisors whom they trust; farmers being ready to ask questions they really want; and who feel community support. Sustainable farming is no longer prescriptive, but is working through the process yourself to find your own specific solution.
- **It is key to implement sustainable management practices as a whole.** Parasite control and preserving anthelmintic efficacy are not silos. Solutions need to be found that improve the sustainability of whole farm operations. Economic sciences offer the tools to identify improvement paths and optimize trade-offs for different (competing) criteria including performance, animal welfare and environmental criteria. We need to see what is the role of sustainable parasite control in the whole farming process.

[4] www.scops.org.uk
[5] www.cattleparasites.org.uk

- Several good tools and knowledge to enable sustainable parasite control are already available. However, the **different techniques need to be married more to obtain successful approaches and provide clear guidelines**. Technology is surely going to play a large part for instance driven by the "smart" or "precision" farming technologies. Targeted Selective Treatment in particular is adept for these rapidly evolving technologies. However, we will still need a lot the "old school" techniques such as simply regularly performing FECs. Uptake of these simple methods can still make a big difference in many situations.

PARTICIPANT FEEDBACK

Feedback from 75 respondents was received over the whole session 2. **Opinions were mixed whether it is easy to find good information on sustainable parasite control** (Figure 4). In addition, it was mentioned that the issue is complex, information can be inconsistent and its availability can vary a lot geographically. **The main obstacles identified to achieve sustainable parasite control** included lack of harmonized guidelines, complexity of the issue and inconsistent information, costs associated with diagnostics and novel practices, low field applicability, drugs that are too cheap and accessible compared with relatively expensive and difficult-to-perform diagnostics, low awareness, communication and education, low evidence base and need for nuanced approaches. International collaborative research was mentioned to be vital to improve communication and dissemination and knowledge exchange between people. **Communication strategies could be improved** by the appointment of dedicated science communicators who are able to translate research findings to farmers, veterinarians and policy makers; through establishing a collaborative network integrating different stakeholders and by identifying hurdles and scientific issues before novel practices are applied. There is a need to pay more attention to the economic and performance impact of recommended measures for livestock farmers. Communication will also depend on accessible control tools that will drive change. Several respondents said it is very important that the solutions for AR are co-created with farmers and other stakeholders in a bottom-up fashion. **Are more regulations needed to address AR?** Some participants argued that if recommended practices are practical and cost-effective, no additional policies are needed. Other proposed they are needed through the development of (inter)national guidelines and/or stricter regulations on the use of anthelmintics such as prescription only use and the prerequisite to treat based on risk and diagnosis. However, guidelines need to be adapted to regional problems and cultures. OIE is currently consulting stakeholders in different continents to prepare guidelines for sustainable use of anthelmintics. It was suggested to include representative(s) from COMBAR and/or the Livestock Helminth Research Alliance (www.lihra.eu) in the OIE guideline committee. Several publicly funded initiatives were deemed highly useful: better frameworks to monitor anthelmintic usage and drug failure, surveillance initiatives for parasites, training opportunities for vets and drug sellers and a flexible attitude towards the use of combination products to delay resistance.

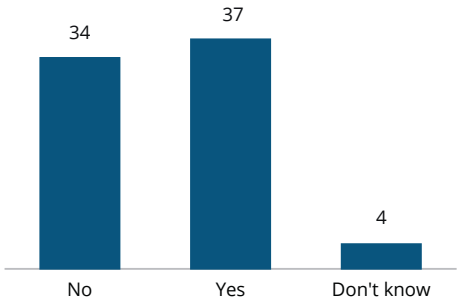


Fig. 4. Participants feedback whether they find it easy to find good information regarding sustainable parasite control.

RECOMMENDATIONS

5. Conduct more social sciences research to understand and drive human behaviour towards sustainable parasite control.
6. Investigate the links between sustainable parasite control with animal welfare, farm economic performance and greenhouse gas emissions from livestock.
7. Establish a framework to bring together all relevant stakeholders around the topic of sustainable parasite control in ruminants. Make these different organisations sit together to move in a common, widely agreed direction, with concrete actions and deliverables, each in their own role and capacity.
8. Produce guidelines at international, national and regional levels that support a proper use of diagnostics and responsible use of anthelmintics. Explore the potential and support base for regulation to implement such guidelines.

SESSION 3

SUSTAINABLE CONTROL

Researchers across Europe have developed a panel of indicators that can be used to optimise anthelmintic usage and slow the development of AR without compromising animal productivity in sheep, cattle and goats. Several experimental anti-helminth vaccines are available and anti-parasitic forages have shown good efficacy in some conditions. Further coordination, experiments and debate are required for these technologies to find their way in real farm situations, how they can be integrated or even replace current practices. COMBAR aims to produce a "basket of options", each with their pros and cons so each available control tool can be used to its maximum potential. Novel control tools may have to be combined to reach optimal efficacy. Their evaluation will depend on the use of predictive models of parasite epidemiology to explore a multitude of scenarios. Moreover, novel approaches should be supported by decision support systems, and economic data to guide effective action by the producer. Ultimately, current advances in diagnostics, economics, social sciences and complementary control tools need to be married to meet the common objectives of sustainable parasite control. These novel control approaches need to be refined and validated in different production and geographical environments.

Work within COMBAR has identified potential interactions between control methods, trained researchers in the use of epidemiological models to evaluate alternative and complementary control methods, and synthesised the challenges in this field in a European setting. During the rest of the action, the basket of options will be further defined and adapted to different European settings. This will improve access to the evidence base on workable solutions to slow AR in ways that are appropriate to geography, livestock sector and farming system.

KEY POINTS OF INVITED PRESENTATION BY DR. BARBARA CYRUS (EMA) – REGULATORY ASPECTS OF NEW ANTHELMINTIC VETERINARY MEDICINES

- The mission of the European Medicines Agency (EMA) is to foster scientific excellence in the evaluation and supervision of (veterinary and human) medicines, for the benefit of public and animal health.
- Across the EU, the same legal basis applies for the Veterinary Medicinal Product (VMP) licensing procedures – Regulation (EC) 2016/6. This new legal framework will come into effect in January 2022. Antiparasitic resistance is much more considered in this new legal framework than before.
- Unique for VMP in livestock compared to medicines for humans and companion animals is that Maximum Residue Limits (MRL) need to be established. This increases costs for registration. Biocides or feed-additives are not evaluated by EMA, but other agencies.
- Authorisation of VMP is based on a benefit-risk balance and involves assessment of a quality (pharmaceutical), safety (for the animal, the user, the consumer and the environment) and efficacy dossier. The Efficacy dossier also includes data on resistance.
- Vaccination is recognised as an alternative, sustainable option for control of helminth parasitic disease, but few are currently on the market (in Europe only the live vaccine against *Dictyocaulus viviparus* in cattle). The very low number of parasite vaccines can be ascribed to the biological complexity, poor understanding of host-parasite interactions and development of immunity, and lack of in vitro production methods that allow scaling up to commercial production. A good overview was recently provided by Claerebout and Geldhof (2020)[6].

[6] *Helminth vaccines in ruminants: from development to application. Veterinary Clinics of North America: Food Animal Practice 36, 159-171.*

- Plant-based antiparasitics follow the same requirements as for standard VMP, but should follow the herbal guidelines [7]. Nematode trapping fungi are considered as biologicals, but no clear guidance is available yet. In such cases, an early dialogue with a licensing authority is highly recommended to discuss these dossiers.
- EMA offers further guidance in preparing a dossier for authorisation of a new product and it is highly recommended to check guidance documents and data on previously conducted tests and trials to avoid unnecessary repetition of tests and obtain the right permission.

PANEL DISCUSSION

Chair: Prof. Eric Morgan (QUB)

Panel members: Dr. Hervé Hoste (INRAE/ENVT), Bruce Thompson (Irish dairy farmer), Dr. Athina Trachili (EAVP), Dr. Thomas Geurden (Zoetis)

- **Where do we stand regarding plant-based therapies, including the use of nematode-trapping fungi?** We have scientific evidence on efficacy, lack of toxicity for the animals, and some knowledge of the mechanisms. In terms of on-farm application a lot more information is still needed on how much and when do we need to administer? We need to better understand the mechanism of action and the secondary metabolites of plants (PSM); to consider the different stage of worms and functions and structure of worms. Toxicity and residues affecting the consumer have also not yet been addressed. This is less of an issue for fungi, but more so with essential oils, particularly in milk or for example cheese processing. Worms could also develop resistance against plant-based therapies and this should be assessed. Further, socio-economic aspects have not been considered so far: end user acceptance and commercial organisation can be a bottleneck. Plant-based therapies have the potential to be applied in a wide range of host species and to be effective against numerous gastrointestinal nematode species. Herbal treatments are in many ways similar to synthetic anthelmintics, but there are differences. Whereas synthetic anthelmintics typically target adult and/or larval stages in the animal, plant-based therapies can also target host responses and free-living stages on pasture. The application can also be different, e.g. through mixing in the diet or integrating in pastures.
- **It is hard for farmers to 'see' resistance and look for alternatives for current practices**, particularly with the risks of changing away from what has proven to work. Most cattle farmers think resistance is still a long way down the road and don't know the implications on economics and animal welfare. So awareness and promotion are important. A particular issue is that advice on alternative approaches is much less readily available. Farmers are not aware of all the tools available. There is the issue of costs and interpreting results, think of complex matters such as refugia management. There is also a confidence issue – horror stories of farmers losing animals by not using products. There is a lack of real time regional parasite information. Diagnostic information could be shared by the diagnostic labs to vets to get a regional real time picture. Still, complex solutions can be accepted by farmers. For instance, resistant animals through genetics (fluke resistance in sires), traffic light grazing and use of dung beetles to clean pastures.
- **The vet / farmer relationship needs a**

[7] *https://www.ema.europa.eu/en/human-regulatory/research-development/scientific-guidelines/multidisciplinary/herbal-medicinal-products-scientific-guidelines*

change of mind: the vet is often only called for sick animals as opposed to paying the vet to keep animals healthy. There needs to be a consultancy role with the vet, to implement a plan at start of the year which is adaptable as the year progresses. The vet is the person who must persuade farmers to consider sustainable control. Vets first need to be convinced and be trained on innovative approaches and testing techniques. If they are properly prepared, they can convince the farmers. It is then the job of the vet to highlight problems to the farmer, the financial losses if the approach is not sustainable, and advise and support in the use of new approaches. Many farmers are keen to work with vets in such a way, but there is need for a legislation/incentives saying every farm must have a vet responsible for treatment and herd health monitoring. The vet should be the animal health scientist at the farm.

- There is always appetite from the industry to start a development programme for something new. However, is there a real need for new anthelmintics? In this forum [i.e. COMBAR], we are a bit biased, but from a market perspective, things are different. New products (e.g. monepantel), don't get adopted wide scale, and farmers are still using the old products (e.g. the benzimidazoles) despite widespread resistance issues. We have been spoiled with broad-spectrum products since the 80's. Now, **a company has to consider how a new product can be developed that is as attractive as those we now use**. Lots of new products are being released for companion animals. In production animals, however, the development costs are much higher - driven by user safety, withdrawal time and environmental safety.
- Customers have evolved from being pleased with treatments to focusing on prevention and management. **In animal health companies, diagnostics is becoming a new focus**, however, it's still a new area for many companies and it has to grow and expand.

PARTICIPANT FEEDBACK

We received inputs from 48 participants on session 3. Important criteria to speak of sustainable parasite control are summarised in a word cloud in Figure 5. Sustainable parasite control should meet the three pillars of sustainability (social, economic, environmental).

Figure 5. Important criteria to speak of sustainable parasite control.

Sustainability was argued to depend on (1) diagnostics to know the parasites you have, (2) diagnostics to know the resistance status of your farm, (3) preventive measures in the form of a plan and (4) selective and controlled use of anthelmintics or other control approaches. **Promising tools to improve future parasite control are on the horizon**. Respondents thought in particular of vaccines and advances in diagnostics. Also new medicines and nutraceuticals were mentioned. The most promising advances in diagnostics are pen-side tests, molecular techniques for rapid species identification and molecular markers for resistance, and automated faecal egg counts. Predictive modelling as well as the growth of on farm technologies examining animal health is a promising avenue. Big data combining parasite infection data with data on farm management, feeding, climate, animal performance is another important area. These can spur the deployment of targeted treatments as well as targeted selective treatment concepts to only those animals/animal groups that are in need of treatment. **Guidelines on sustainable parasite control needed to be evidence-based and as concise, practical and easy to understand as possible.** SCOPS and COWS in the UK were considered good examples that could inspire other countries. Flexibility and holistic were two other key words and referred to the need for adaptability to differing farming, environmental and cultural contexts and for considering that parasites are only one of many issues that need to be sustainably managed on farm. In general, guidelines should support broader farm management plans on animal health in general. Guidelines need consultation of needs and involvement of all stakeholder organisations. They need to be supported by a lot of communication and teaching. Novel video- and web-based techniques should be considered for these.

RECOMMENDATIONS

9. Conduct research towards host-parasite interactions and development of immunity to speed up vaccine development using methods fit for commercial production.
10. Increase research efforts towards mechanisms of action of plant-based therapies.
11. Consult with end-users which novel parasite control methods are viable and invest in training, promotion and dissemination.
12. Use new technologies (“omics”, big data) for next generation diagnostics and decision support systems on parasite infection.
13. Invest in the vet/farmer relationship and provide incentives towards a stronger role for the vet in disease prevention.

APPENDICES

APPENDIX 1

RECOMMENDATIONS EMERGING FROM THE 4TH COMBAR JOINT WG MEETING

RESEARCH

1. Upsurge implementation of "omics" approaches to unravel molecular mechanisms underpinning AR and lever the development of cost-effective *in vitro* and molecular tests for AR.
2. Use new technologies ("omics", big data) for next generation diagnostics and decision support systems on parasite infection.
3. Conduct research towards host-parasite interactions and development of immunity to speed up vaccine development using methods fit for commercial production.
4. Increase research efforts towards mechanisms of action of plant-based therapies.
5. Investigate the links between sustainable parasite control with animal welfare, farm economic performance and greenhouse gas emissions from livestock.
6. Increase research efforts and harmonize investigational approaches on helminth infections and AR in Southern and Eastern European countries, where knowledge of epidemiology, AR and control of helminth infections is poor relative to other European regions.
7. Conduct more social sciences research to understand and drive human behaviour towards sustainable parasite control.

COORDINATION

1. Develop multi-actor approaches involving veterinarians, farmers, pharmaceutical industry and research bodies to create awareness and identify solution paths in mitigating the escalating spread of AR.
2. Establish a framework to bring together all relevant stakeholders around the topic of sustainable parasite control in ruminants. Make these different organisations sit together to move in a common, widely agreed direction, with concrete actions and deliverables, each in their own role and capacity.
3. Train the trainers: develop training programmes to empower veterinarians and herd advisors in understanding the complex epidemiology of parasitic helminth infections and delivering evidence-based advice to farmers.

COMMUNICATION

1. Produce guidelines at international, national and regional levels that support a proper use of diagnostics and responsible use of anthelmintics. Explore the potential and support base for regulation to implement such guidelines.
2. Consult with end-users which novel parasite control methods are viable and invest in training, promotion and dissemination.
3. Invest in the vet/farmer relationship and provide incentives towards a stronger role for the vet in disease prevention.

APPENDIX 2
MEETING PROGRAMME

Wednesday 09/12/2020

10:00-12:00	COMBAR 5th Management Committee (MC) meeting	MC members only

Session 1	Improving diagnosis	Chair: Laura Rinaldi (UNINA)
14:00 - 14:10	Introduction	
14:10 - 14:40	**Keynote: Monitoring anthelmintic resistance: from phenotypic assays to molecular markers.**	Cédric Neveu (INRAE)
14:40 – 14:52	Survival of the fittest? Ecological fitness assessment in *Teladorsagia circumcincta* of known anthelmintic resistance status.	Kyra Hamilton (Teagasc)
14:52 – 15:04	Transgenically expressed *Haemonchus contortus* Cyp HCOI00827700 can modulate ivermectin susceptibility in *Caenorhabditis elegans*.	Natalie Jakobs (FUB)
15:04 – 15:16	Bulk tank milk *Ostertagia* ELISA as a tool for quantification of milk production losses in dairy herds : where do we stand?	Nadine Ravinet (Oniris)
15:16 – 15:25	**One – minute poster presentations** on droplet digital PCR for levamisole resistance screening, anthelmintic efficacy in Germany, the new Kubic FLOTAC microscope, *Dictyocaulus* bulk tank milk ELISA.	Presenters from SLU, FUB, UNINA and UGent
15:25 - 16:00	**Moderated discussion** with contributions from Georg von Samson Himmelstjerna (FUB), Smaro Sotiraki (HAO Demeter), Menno Holzhauer (Royal GD Deventer) and Eurion Thomas (FECPAK).	

Thursday 10/12/2020

Session 2	Socio-economics	Chair: Edwin Claerebout (UGent)
10:00 - 10:10	Introduction	
10:10 - 10:40	**Keynote: OIE's activities on antiparastics resistance.**	Maria Szabo (OIE)
10:40 – 10:52	Initial assessment of the economic burden of major parasitic helminth infections to the ruminant livestock industry in Europe.	Johannes Charlier (Kreavet)
10:52 – 11:04	Barriers and incentives for uptake of diagnostics for sustainable worm control by European dairy cattle farmers.	Fiona Vande Velde (UGent/ NMBU)
11:04 – 11:16	Treatment against helminths in Norwegian sheep – a questionnaire-based survey.	Maiken Gravdal (NMBU)
11:16 - 11:25	**One minute poster presentations** on producer knowledge, effect of anthelmintic treatment on milk yield in sheep, ML resistance in Brazil.	Presenters from Universidade de Évora, University of León, Federal University of Parana
11:15 - 12:00	**Moderated discussion** with contributions from Dave Bartley (MRI), Lesley Stubbings (SCOPS), Erwin Wauters (ILVO) and Katarina Gustafsson (Farm and Animal Health, Sweden).	

Session 3	Sustainable control	Chair: Eric Morgan (QUB)
14:00 - 14:10	Introduction	
14:10 - 14:40	**Keynote: Regulatory aspects of new anthelmintic veterinary medicines.**	Barbara Cyrus (EMA)
14:40 – 14:52	*In vivo* anthelmintic efficacy of aqueous *Dryopteris filix-max* and *Punica granatum* macerates against gastrointestinal nematodes of sheep.	Fabio Castagna (University of Catanzaro)
14:52 – 15:04	A diluting strategy to reduce anthelminthic treatment: suckling dairy calf/nurse cow system and gastrointestinal infection during the first grazing season.	Christophe Chartier (INRAE/ Oniris)
15:04 – 15:16	Efficacy of vaccination against *Teladorsagia circumcincta* in two native sheep in Gran Canaria is conditioned by age and breed.	Cynthia Machin (Universidad de Las Palmas de Gran Canaria)
15:16 – 15:25	**One minute poster presentations** on FAMACHA©, evaluation of seaweed, essential oils and nematode-killing bacteria for nematode control	Presenters from Instituto Nacional de Investigação Agrária e Veterinária Portugal, University of Copenhagen, University of Novi Sad, University of Ljubljana
15:25 - 16:00	**Moderated discussion** with contributions from Hervé Hoste (INRAE/ENVT), Bruce Thompson (Irish dairy farmer), Athina Trachili (European Association of Veterinary Practitioners) and Thomas Geurden (Zoetis).	

APPENDIX 3

STATISTICS OF THE EVENT

REGISTRATIONS AND PROFESSIONAL BACKGROUND OF THE PARTICIPANTS

The number of registered people for the meetings was 285. Their professional background is given in figure A.1. Of these, 268 attended at least one of the 3 sessions with 186 participants in session 1, 157 in session 2 and 166 in session 3. Fourty-one percent of the registrants were early-career investigators (less than 8 years after obtaining PhD).

Fig. A.1. Professional background of the meeting participants

HOW THE PARTICIPANTS HEARD ABOUT THE EVENT

Most participants were reached via mouth-on-mouth dissemination, followed by direct e-mail and other media (Fig A.2)

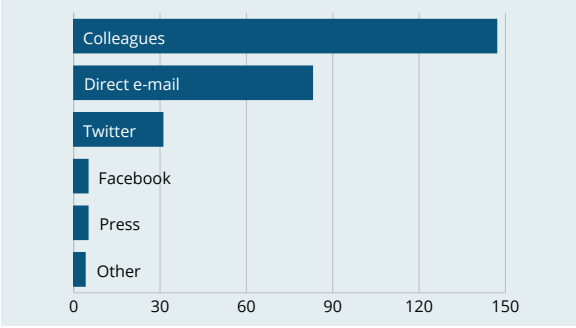
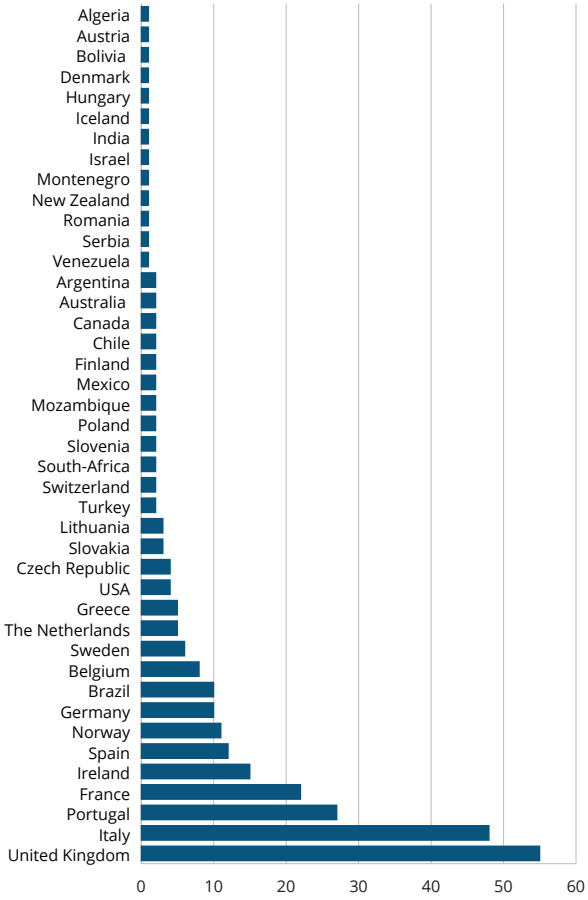


Fig. A.2. Main communication channels of the event.

PARTICIPATING COUNTRIES

Participants came from 42 different countries. Most participants came from the UK, followed by Italy, Portugal and France. However, there were participants from all regions in the world.



WWW.COMBAR-CA.EU