RESISTANCE OF ECTO- AND ENDOPARASITES: CURRENT AND FUTURE SOLUTIONS

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Summary: The Office International des Epizooties (OIE) conducted a survey to determine the importance of the problem of resistance of ecto- and endoparasites to the most commonly used chemical compounds and to establish possible approaches for preventing and controlling resistance.

Based on the replies from 77 OIE Member Countries (52%), it was revealed that those ecto- and endoparasites with the heaviest relative impact on production are also those that present the widest distribution of resistance. In 55% of the countries, resistance to antiparasitic agents has been diagnosed in at least one group of parasites included in the study. Eighty-six per cent have diagnosed resistance to antihelmintics, 50% to ixodicides, 31% to insecticides (Diptera of veterinary importance), 19% to acaricides used against mange and 10% to acaricide used against lice. Twenty-four per cent of the countries have resistance in more than three groups of parasites and 22% have it in the two groups of parasites considered to be of greatest economic impact. The risk of developing resistance in non-target species, through the indiscriminate use of antiparasitic agents, is discussed in this report.

In spite of the publicity that has been given to the resistance phenomenon over the past decade, the approach to its prevention and control has not altered substantially. Those countries which take some measures to prevent and control resistance are doing so almost exclusively by changing or rotating antiparasitic agents.

According to the information provided by the Veterinary Services of the Member Countries, there is a critical and pressing need to involve all parties - governments, the pharmaceutical industry and private and international organisations - in developing sustainable and economically viable programmes to combat parasitic diseases in general, and resistance to antiparasitic agents in particular. These programmes should be made an integral part of the routine animal health interventions carried out by Veterinary Services.

1. INTRODUCTION

The development of increasingly effective drugs that are capable of controlling a large number of parasite species has, without doubt, been one of the most impressive technological achievements of the twentieth century. The systematic use of relatively inexpensive antiparasitic agents that are effective and easy to apply has made it possible to control pests that affect animal and plant health in the widest range of production systems.

The continuous development of new compounds by the pharmaceutical industry has been as exciting as it has been disturbing: stimulating, because of the whole range of possibilities for preventive and/or curative application to control economically important parasitic diseases, but at the same time worrying, because of the possibilities of developing resistance, creating ecological imbalances (22, 45), and leaving residues in meat, milk and wool. Indeed, the development of resistance is intricately linked to increased treatment frequency and dosage. This enhances the possibility of residues and could turn into a non-tariff barrier to trade between countries (29, 39, 48). Another situation preventing trade, both within and between countries, is the possibility of introducing resistant parasites through the transfer (36, 43) or import of live animals. This is a widely recognised fact in the case of arthropods and is becoming more frequent in helminths (15, 24, 39, 41, 55).
In this decade, nearly one century after the first reports of arthropod resistance to pesticides for agricultural use (32), an almost exponential increase in new cases of resistance in the parasite species is occurring, affecting agriculture and public health in various geo-climatic areas of the world (23, 42, 52). Even microbiological resistance to antibiotics for human and animal use is now a problem, for which it is imperative to develop coordinated guidelines for prevention and control (3).

This transformation in the genetics of parasite populations has developed within a world context of far-reaching political, social and economic change, which must be taken into consideration when attempting to implement sustainable prevention and control measures. The scenario for the twenty-first century will be characterised by meat, wool and milk markets that are ever more globalised, competitive and demanding, especially with regard to residues and environmental contamination. Governments and industry will not have the same operational freedom as in the past and it is unlikely that there will even exist a drug to which parasites cannot develop resistance.

The aim of the OIE study was to analyse the impact on production ascribed, by OIE Member Countries, to the problem of ecto- and endoparasites in general, and of resistance to antiparasitic agents in particular. Within this frame of reference, consideration will be given to the possible approach to be taken at national, regional and international level in order to control the problem and prevent it from escalating, as well as to secure the sustainability of animal production systems. Out of a total of 151 OIE Member Countries (1998), 77 responses to the questionnaire were received and analysed (Table 1), which represents a 51% of the sample.

2. PRODUCTION CONTEXT AND RESISTANCE TO ANTIPARASITIC AGENTS

The economic importance of the resistance phenomenon is intricately linked with the causal agent’s distribution, prevalence, incidence and impact on local production. This report considers parasitic agents that are widely distributed throughout the world, such as some species of arthropods (namely ticks, mange mites, Diptera and lice) and helminths, placing special emphasis on those with the greatest impact on animal production and productivity in the Member Countries.

The complexity of determining the direct and indirect impact of parasitic diseases on production is reflected in the report. Unfortunately, much of the available information concerning production and economic losses does not yet cover all parts of the world, and more than 65% of the countries surveyed have not carried out any such studies, with the result that estimates were based on the experiences of the Veterinary Services and their perception of economical importance.

Table 1: OIE Member Countries participating in the study concerning the resistance of ecto- and endoparasites to chemical compounds

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The parasitic diseases were divided into four categories according to their economic production importance and the potential for resistance development. The replies were divided into four categories According to the production/economic importance of parasitic diseases and the development of resistance (Figure 1). Of this group, 56 countries cited helminths as being the most significant problem, 15 ticks, 4 Diptera, 1 mange mites and none lice. Notwithstanding the clear preponderance of helminthiasis, many countries cited the tick as the leading pest (n = 28) and the mange mite (n = 14) as the second most important pest. For a more accurate profile of the Member Countries’ perceptions concerning the relative importance of parasitic diseases, the diseases included in the first, second, third and fourth categories were weight-ranked. This resulted in helminths being assigned 38.9% of the total points for all categories; ticks, 23.7%; mange mites 15.4%; Diptera of veterinary importance, 15.2%; and lice, 6.8%.

With very few exceptions, chemical compounds have been the sole means used by agricultural and livestock producers for controlling parasitic diseases. For this reason, comparing the market for antiparasitic agents with that for other consumables (antibiotics, vaccines, sera) is a good indicator of the relative importance attributed by the countries to these agents: 85.7% of the countries consider that they have a significant market for antiparasitic agents, either for the combined control of ecto- and endoparasites (57.1%), or for the sole control of endoparasites (18.2%) or the sole control of ectoparasites (10.4%); 14.3% of the countries consider the market to be insignificant compared with that for other biologicals.

Veterinary Services’ perception is generally consistent with the sale of antiparasitic agents used for domestic animals. In 1997, world sales of endoparasiticides (36%) endectocides (25%) and ectoparasiticides (39%) were in the region of USD 3,100 million (54). The demand for antiparasiticides differs from one geo-economic area to another: depending on production systems and parasite populations. However, what remains the key issue is that a moderate loss of efficacy (generally not perceived at field level) represents an enormous loss in terms of the antiparasitic agent’s cost-effectiveness, and a significant step along the path of no return in terms of parasite resistance. For example, a reduction of 20% in the efficacy of an anthelmintic or acaricide at field level not only means a loss of efficacy equivalent to USD 20 for every USD 100 invested in veterinary products, but also represents a genetically based problem with regard to the future sustainability of the whole chemical group.

![Figure 1: Veterinary Services’ perception of the relative importance of ecto- and endoparasites that develop resistance to antiparasitic agents](image-url)
3. DIAGNOSIS AND RESISTANCE

Disease diagnosis and control are two inseparable issues in any health programme; in the case of resistance to antiparasitic agents, the relationship between diagnosis and control becomes even more crucial. In this case, it is not sufficient to merely know the causal agent, it is also necessary to determine, as early as possible, the degree of sensitivity of the parasite populations to the available chemical groups (collateral, cross, or multiple resistance).

For ectoparasites (23) and endoparasites (27), resistance to drugs has, with a few variations, been defined in such a way as to be consistent with the definitions proposed by the WHO’s Committee of Experts on Insecticides in 1957, and the FAO’s Group of Experts on Resistance3 in 1967 (18). The definition of resistance used in this report is: the detection, by means of sensitive tests, of a significant increase in individuals within a single species and population of parasites that are capable of tolerating doses of drug(s) that have proven to be lethal for most individuals of the same species.

In the survey, 54.5% (n = 42) of the countries replied that they had diagnoses of resistance in at least one group of parasites included in the survey and 36.4% of the countries (n = 28) had no diagnosis of resistance. It was not possible to take the remaining 9% (n = 7) of countries into consideration, due to the lack of a clear response concerning the techniques used. There is almost certainly under-recording of these figures, as the resistance of some groups of parasitic diseases, such as helminthoses, are not normally reported to Veterinary Services.

Out of the total number of positive replies, 86% (n = 36) corresponded to diagnoses of helminths, 50% (n = 21) of ticks, 31% (n = 13) of Diptera, 19% (n = 8) of mange mites and 10% (n = 4) of lice. These results show overlapping of the resistance phenomenon, with 22% of countries classifying two groups of parasites - helminths and ticks - to be of greatest production/economical importance. It was also observed that 24.4% (n = 10) of the countries have to cope with the problem of resistance in more than three groups of parasites (range = 3-5) included in this study.

This latter fact has only rarely been taken into account when a disease problem is considered at field level and disease control must be planned hurriedly. It is increasingly frequent for the producer to experience 'multi-resistance', which has developed simultaneously, not only to several groups of antiparasitic agents (53), but also in different species of parasites (e.g. Haemonchus contortus + Trichostrongylus colubriformis + Ostertagia circumcincta) (16, 17). The exposed populations are sometimes composed only of ticks (e.g. Amblyomma variegatum + Boophilus microplus) (48), or of ticks and Diptera (B. microplus + Haematobia irritans) (11, 31, 53).

Accordingly, any rational disease control programme should start by using this knowledge to develop the disease capabilities to differentiate the effect of the antiparasitic agent on the target species for disease control purposes from those non-target species affected by the antiparasitic agent. In many cases, the most pathogenic parasite species with the greatest potential for survival are those that determine the frequency of treatments applied by the producer. This situation was confirmed recently in some temperate areas of South America, where H. contortus is the most important parasite for the producer, but the most serious problem of resistance is that of T. Colubriformis, which has been unnecessarily under pressure by the use of broad-spectrum anthelmintics (36, 37). The increasingly frequent use of endectocides in many of the world’s production areas may compound this trend.

A lack of diagnosis does not mean that the problem does not exist; on the contrary, it often indicates a series of shortcomings, ranging from a failure to perceive the problem in the field, to the lack of capabilities to carry out laboratory diagnosis. Analysing the reported diagnostic difficulties, 27.3% of the Member Countries believe that there is a lack of understanding or interest in the resistance problem among agricultural and livestock producers, which may delay the process of diagnosis and reporting. Without doubt, the producer’s aptitude (training) is a decisive factor in his/her attitude to the problem. The most modern and successful programmes for controlling agricultural pests consider the training of producers to be the first priority in controlling crop parasites (20).

Another difficulty that has been of concern to the Member Countries is the lack of the required infrastructure for the flow of disease information from the field to the laboratories to link health problems occurring in the field with the laboratory. In 27.3% of replies (principally from developing countries), this is considered to be the worst problem associated with the early detection of resistance. This situation underlines governments’ lack of information on the real impact of health problems and hinders the planning of proper control measures (21, 40).

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1 WHO: World Health Organization
2 FAO: Food and Agriculture Organization of the United Nations
3 FAO: Food and Agriculture Organization of the United Nations
The lack of proper techniques for diagnosing resistance was stated by 26.0\% of the countries to be the main difficulty when it comes to maintaining a resistance-monitoring system. This issue has attracted the attention of governments, international institutions and academic organisations (9, 28). In the case of ticks, it was one of the principal objectives of the FAO’s World Acaricide Resistance Reference Centre (WARRC) in Berlin, Germany (48). Unfortunately, this Centre has been defunct since 1996 due to funding problems, the functions that were formerly carried out by WARRC will have to be included in any future plans for global acaricide monitoring.

Finally, Member Countries commented on the lack of research capability for the resistance phenomenon in animal health. This is a situation that has been worsening in recent years, and which completes the vicious circle of a lack of alternatives for reducing dependency on drugs (21, 28, 34).

4. CURRENT FRAME OF REFERENCE FOR THE CONTROL AND PREVENTION OF RESISTANCE

In theory, any population of parasites can develop resistance to any chemical compound or group of compounds. For controlling resistance, changing the active ingredient seems to have worked, where new antiparasitic agents have appeared on the market and/or the prevalence of resistance has been imperceptible. On many occasions, livestock producers changed the drugs they were using without a resistance diagnosis being made. However, often the change was in trade names but not in the active ingredient (33). On other occasions one active ingredient was exchanged for, on a massive scale, for another, because of rumours and not because of resistance diagnosis. Again only the trade names were changed and not the active ingredient. An example of this situation was the changeover from organophosphorous acaricides to pyrethroid acaricides to control *B. microplus* (8, 31), and the massive change to generic ivermectins or avermectins for sheep, without first confirming resistance to the bencimidazole and levamisole groups (30).

Today it is clear that, for both ecto- and endoparasites, the problem is not the use of antiparasitic agents themselves as a means of control, the 'original sin' in this process is due to human nature, as the user will always be inclined to simplify the control routine by using the most effective and easiest means at hand (33, 47). The great efficacy, broad spectrum and prolonged residual power of many antiparasitic agents have increased the producer’s sense of security, discouraging diagnosis and professional support. The gradual process of 'substitution', first of diagnosis and later of professional advice, has been particularly apparent in the control of gastrointestinal nematodes and of ticks/Diptera.

It would appear that the prevention and control approach has not changed substantially. Of the 42.9\% of countries that declare themselves to have developed some type of control of resistance, 84.9\% did so exclusively by changing drugs and only 15.1\% mention other types of measures. Of the countries that carry out resistance prevention measures, 64.9\% do so mainly by rotating chemical groups, although some countries do recognise and stress the importance of education in order to prevent the problem from escalating.

In the near future, it will be difficult to maintain a prevention and control approach based almost exclusively on the use of antiparasitic agents, due to the fact that:

- **No permanent supply of new drugs is foreseen.** The pharmaceutical industry has suffered continually escalating research and development costs for the registration of new drugs. The cost of developing a new product is between USD 100 and 230 million, for a process that can take more than 10 years from discovery of a potential candidate, to placing it on the market (12, 46). Another important transformation that has occurred in the pharmaceutical industry has been the world trend towards consolidation and integration, which has had some effect on research into effective new compounds. The Animal Health Institute (AHI), a trade association representing 80\% of the veterinary products in the United States of America, has reported that today there remain only 27 or so of the 60 member companies that existed 20 years ago, with no more than a small number of these retaining research and development capabilities. Antiparasitic compounds have to compete for funding with products that benefit other more profitable patients, specifically humans (46). Thus, the antiparasitic agents for use in animal health must be viewed as a non-renewable resource.

- **Government Veterinary Services are undergoing an important transformation.** In many cases, it is difficult to maintain a specialised 'critical mass' and adequate facilities to support the registration and continual quality control of antiparasitic agents at Government level. Of the countries included in this study, 49.3\% (n = 38) admitted having difficulties in ensuring proper registration of antiparasitic agents. This basic government function is fulfilled with great difficulty in developing countries, which are much more susceptible to problems of adulteration and the introduction of low-quality drugs. The principal difficulties mentioned by the Member Countries include: lack of proper legislation; lack of a specific registration unit; registration by other government units not specialised in animal health; total or partial lack of infrastructure to carry out the necessary analytical
testing for each type of compound; the impossibility of ensuring continuing control over the quality of antiparasitic agents; and the failure to link registration with the occurrence of resistance in the field. Generic antiparasitic agents have come to stay. It is not difficult these days to find countries where the same active ingredient is marketed under more than 20 different trade names. Price and formulations competition are healthy, provided of course that quality is maintained (which does not only mean the correct concentration of the active ingredient). This situation and the lack of training among users increase the consumption of cheap and often low-quality drugs. Without doubt this is the great challenge facing countries that do not yet have the capability to control the toxicity, residues and efficacy of antiparasitic agents.

5. CURRENT AND FUTURE MEASURES

The need to involve all of the parties involved - governments, the pharmaceutical industry and private and international organisations - in developing a sustainable and economically viable programme to combat parasitic diseases in general, and resistance in particular, has become ever more crucial.

5.1. Regional and national spheres

Sustainable disease control will not be possible unless there is sustainable national production systems (14, 44). This is especially true for developing countries where examples abound of institutions and agencies wrongly imposing methods that were perceived as 'superior', but which were, in fact, ill-adapted to local climatic, social, economic and productive conditions (2). In the twenty-first century, it therefore appears reasonable to require that developing countries and those in transition maintain a small critical mass of specialised professionals to manage the problem of resistance at four basic levels:

**Diagnosis:** Diagnosis is one aspect of the global management of resistance (28). It is necessary to establish the capability, or strengthen the existing capability, for diagnosing resistance using duly standardised and harmonised techniques, making it possible to rationalise control measures without the indiscriminate use of antiparasitic agents.

**Epidemiology:** There is no more crucial requirement for the rational management of grazing animals than knowledge of the epidemiology of local parasites, which encompass all of the variables that help to prevent or to favour parasite development (5, 35). Epidemiology is the frame of reference on which the rational control of resistance must be based. Although the importance of epidemiological knowledge in the prevention and control of resistance to antiparasitic agents is widely accepted, much still remains to be learned about the process of genetic variation of parasite populations 'inside' and 'outside' their host populations. The availability of molecular techniques and appropriate mathematical models will provide a better understanding of the genetic evolution of parasite populations and help to minimise selection for resistance (1). Here again, developing countries must make an effort to maintain a small critical mass of professionals (quality, not quantity) who are capable of understanding and validating the new technological advances locally.

**Integrated pest management:** Total dependence on a single method of control has not proven to be non-sustainable and non-cost-effective in the long term (14, 25, 50, 51). In terms of control of parasite resistance, integrated pest management (IPM) effectively combines several means of control as a way to destabilise those parasite populations with the largest proportion of individuals that are genetically resistant to antiparasitic agents. For this reason, IPM is generally associated with a reduction in the frequency of treatments, as in a number of studies, a strong association has been observed between treatment frequency and the development of resistance (38). Nevertheless, the reverse is not necessarily true, as at least for gastrointestinal nematodes, the selection pressure exercised by the treatment will depend on the potential for dilution refugia populations sheltered (4). For parasites with naturally large refugia populations (e.g. gastrointestinal Nematoda and ticks), special epidemiological conditions, such as an unfavourable season in extreme climates, an intense drought, or pasture management to reduce these populations, can dramatically alter the selection pressure of the treatment. The mange mite, as an obligate parasite with practically no refugia population, is a natural example of how resistance can develop as a result of simultaneously exposing all parasitic stages to the treatments. So, when implementing an IPM programme, it is not sufficient merely to use fewer treatments; instead, the treatments must be carried out in accordance with seasons/times/animals, allowing greater dilution of parasite populations (7). This is the principle underlying the FAMACHA4 technique, originally developed in South Africa to control *H. contortus* in sheep (49).

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4 FAMACHA: Faffa Malan Chart
At present, the FAO is cooperating with the validation of this technique in the field in Paraguay, South Africa and Uruguay.

The implementation of an IPM programme involves some important elements that are sometimes difficult to achieve in developing countries. These include the availability of results from applied research; a change of policy to foster the application of methods that are less dependent on antiparasitic agents; and the participation of the producer and his veterinary advisor in training programmes. Some IPM systems are complicated to implement, but the routine use of computerised models makes it possible to rationalise control measures in a more global and economical manner (6, 10, 26).

There are three levels where IPM can be used: the first is to control a parasite species (e.g. ticks); the second to control two or more species that coexist in the host (e.g. ticks + transmitted diseases + H. irritans); and the third is through integration with rural development (e.g. tsetse + trypanosomiasis).

Registration and control of antiparasitic agents: It is during the registration process that the competent government authority approves the sale and use of an antiparasitic agent, after having evaluated whether the product is effective and that its use involves no risk to animals, public health or the environment. Principally the main difficulty for developing countries is the analysis for certification of a large variety of antiparasitic agents, not only because of the sophisticated infrastructure that is required, but also because specialised personnel are required to carry out the tests. Notwithstanding this, some countries have made important advances both nationally and regionally, so it is assumed that those countries with fewer resources will be given support in the future. Following this extremely important step is another that is perhaps more complicated to implement and for which the poorer countries are on their own: that is the continual monitoring of the quality of antiparasitic agents in order to prevent abuses, including adulteration, the sale of batches of substandard drugs, the administration to animals of compounds for agricultural use, 'homed made' preparations and drug combinations of dubious stability. For countries with other emergencies to deal with, it is no easy task to establish or reinforce these two activities, which is why this requires a long-term commitment, accompanied by intensive training for the user.

5.2. International sphere: Food and Agriculture Organization of the United Nations integrated knowledge

Many of the measures against ecto- and endoparasites have been aimed at improving diagnostic capability and epidemiological knowledge as a basis for the use of cost-effective and sustainable systems of control. In 1956, the FAO and the OIE, concerned with the increase in the incidence of ticks and the movement of animals, organised the first 'Consultation of Experts on Ticks and Tick-Borne Diseases they transmit'. Since then a series of further measures have followed, including support for integrated programmes to control ticks and tick-transmitted diseases in Africa, the eradication of *Amblyomma variegatum* in the Caribbean, and several Expert Consultations which were reviewed by de Castro (13, 14) and Thullner (48).

In 1991, the First Consultation of Experts on Helminthic Infections was held, one of the specific objectives of which was to evaluate resistance to anthelmintics in ruminants (19).

More recently, in the field of prevention and control of resistance to antiparasitic agents, the FAO’s Animal Health Service, together with its Regional Offices, have made advances with some international measures, which will be summarised below.

A working group was established in 1997, called the 'Working Group on Parasite Resistance' (WGPR). This is a panel of experts that advises the FAO on strategies for integrated pest management (IPM) and resistance management. The WGPR gathers, organises and analyses information on the epidemiology, diagnosis and control of parasites and management of resistance to parasites, assisting the FAO in preparing guidelines for its diagnosis and control.

The WGPR works in constant collaboration with the pharmaceutical industry by means of an FAO/Industry Contact Group. Industry is represented by the Veterinary Parasite Resistance Group (VPRG), a COMISA specialised consultative group whose mandate is to advise industry and non-industrial organisations on the implications and consequences of resistance to parasites, and on monitoring and control strategies (R. Curtis, pers. comm., 1998). The VGRP currently includes eight of the world’s leading companies that conduct research and development on antiparasitic agents.

As a follow-up to the WGRP’s recommendations, the FAO has promoted and financed the creation of three electronic networks on ecto- and endoparasites, which will be completely operational by around mid-1999. Two networks on helminths have been set up - one in Latin America (coordinated by INTA®), Castelar, Republic of

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5 COMISA: World Animal Health Industry Confederation
6 INTA: Instituto Nacional de Tecnología Agropecuaria
Argentina) and the other in Africa (coordinated by the Veterinary Faculty of Pretoria, South Africa). The network on Ticks and Tick-Borne Diseases is coordinated by CORPOICA7 in Bogota, Colombia. In addition to the specific functions performed by these networks, the FAO will encourage interconnection and interaction between these and other existing networks.

In the area of ectoparasites, three References Centres for the Diagnosis and Control of Ticks have been set up in Latin America to partially assume the activities formerly carried out by the FAO’s World Reference Centre. The three Centres are regional in scope and are located in Colombia (CORPOICA), Mexico (CENID-PAVET8) and Uruguay (DILAVE ‘Miguel C. Rubino9). During the first phase, the Centres have the task of developing the region’s technical capability for diagnosing and monitoring tick resistance to acaricides. The activities of the Centres will be disseminated through the corresponding network, which will also provide timely information on training courses, seminars and working meetings and the availability of duly harmonised and standardised diagnostic 'kits'. In short, the aim of all of these measures is to provide the required conditions and information for the development of sustainable IPM and the appropriate management of resistance to parasites.

REFERENCES


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7 CORPOICA: Corporación Colombiana de Investigación Agropecuaria
8 CENAPA: Centro Nacional de Investigaciones Disciplinarias en Microbiología
9 DILAVE: Dirección de Laboratorios Veterinarios "Miguel C. Rubino"


