Food and Agriculture Organization of the United Nations

Expert consultation on the sustainable management of parasites in livestock challenged by the global emergence of resistance

Virtual meeting
9–10 November 2021

Part 1: Current status and management of acaricide resistance in livestock ticks

FAO ANIMAL PRODUCTION AND HEALTH / **REPORT 17**

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Published by
FOOD AND AGRICULTURE ORGANIZATION OF THE UNITED NATIONS
Rome, 2022

Required citation:
FAO. 2022. *Expert consultation on the sustainable management of parasites in livestock challenged by the global emergence of resistance – Part 1: Current status and management of acaricide resistance in livestock ticks, 9–10 November 2021*. FAO Animal Production and Health Report No. 17. Rome. https://doi.org/10.4060/cc2981en

ISBN 978-92-5-137216-6

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Acknowledgements

The Food and Agriculture Organization of the United Nations (FAO) would like to express its appreciation to those who contributed to the expert consultation.

FAO would like to thank the speakers: Guilherme M. Klafke, Patrick Vudriko, Srikanta Ghosh, Nicholas Jonsson, Adalberto Á. Perez de Leon, Roger Ivan Rodriguez-Vivas, Abel S. Biguezoton, Nkululeko Nyangiwe, Juergen Langewald and Christine Maritz-Olivier. Furthermore, we would like to thank Guangyan Liu from the Lanzhou Veterinary Research Institute in China for his sharing his contribution ahead of the meeting. The report was drafted by Frans Jongejan.

Keith Sumption is thanked for his vision and encouragement, which led to the expert consultation. Frans Jongejan, Junxia Song, Weining Zhao, Giuliano Cecchi, Yu Qiu and Jieun Kim are gratefully acknowledged for their valuable contributions to the FAO Parasite Task Force, which led to the successful expert consultation. The attendees are thanked for providing very useful comments in the Q&A.

Thanks also to Claudia Ciarlantini, Cecilia Murguia and Fallon Bwatu for supporting the virtual event in various ways.

Abbreviations and acronyms

AChE	Acetylcholinesterase
AIT	Adult immersion test
AMR	Antimicrobial resistance
CIRDES	*Centre international de recherche-développement sur l'elevage en zone subhumide*
CJWZ	Joint Zoonotic Disease and AMR Center
FAO	Food and Agriculture Organization of the United Nations
GABA	y-Aminobutyric acid
HRM	High-resolution melt
IRAC	Insecticide Resistance Action Committee
IVM	Ivermectin
LIT	Larval immersion test
LPT	Larval packet test
LTT	Larval tarsal test
ML	Macrocyclic lactones
OP	Organophosphates
PCR	Polymerase chain reaction
RF	Resistance factor
SNP	Single nucleotide polymorphisms
SP	Synthetic pyrethroids
TBD	Tick-borne diseases
USDA	United States Department of Agriculture
WHO	World Health Organization
WOAH	World Organisation for Animal Health (formerly acronymized as OIE)

Executive summary

The Food and Agriculture Organization of the United Nations (FAO) organized a virtual expert consultation on 9–10 November 2021 on the sustainable management of parasites in livestock challenged by the global emergence of resistance. The Consultation focused on acaricide resistance in ticks and trypanocidal drug resistance in livestock. This report is based on the first day of the Consultation, whereas part 2 focused on managing trypanocidal drug resistance.

The expert consultation attracted 120 attendees worldwide, particularly from areas most affected by acaricide-resistant ticks, e.g. Brazil, Ecuador, India, Mexico, the southern United States of America and sub-Saharan Africa. Academic and research institutions in Asia, Europe, and North and South America participated. Twenty participants attended from FAO and the other Tripartite organizations: the World Organisation for Animal Health (WOAH) and the World Health Organization (WHO). Government institutions, private-sector representatives and donor agencies also attended the meeting.

Ten international speakers shared their experience regarding the global emergence of acaricide resistance in livestock ticks, which negatively affects the livelihoods of millions of livestock producers. The purpose of the expert consultation was to provide FAO with a global overview of the updated situation regarding the sustainable management of livestock ticks and enable FAO to re-enter the area of ticks and tick-borne disease-affected livestock in the (sub) tropics.

In addition to animal health risks and production losses, there are also human health risks due to handling acaricides and environmental concerns over acaricides. Concerns were raised regarding the extensive use of antibiotics to prevent the transmission of some of the major tick-borne diseases affecting livestock in the (sub) tropical regions.

The main conclusions from the meeting regarding the management of acaricide-resistant livestock ticks were as follows:

- Acaricide resistance in livestock ticks has emerged across the (sub) tropical regions of the world, where it negatively affects the livelihoods of millions of small-scale producers.
- The ability of ticks to develop resistance against different classes of acaricides is aggravated by malpractices in the application of acaricides, use of substandard products, and by the lack of strategies to delay selection for resistance to the acaricidal compounds.
- Currently, there are no commercially available validated diagnostic tests to differentiate between malpractice in chemical tick control and the development of resistance.

- There is much to gain by implementing sustainable tick control strategies wherein conventional acaricides are combined with host resistance to ticks, anti-tick vaccines and natural repellency compounds.

The following recommendations were made to member countries and national authorities:

- Develop and implement stakeholder-owned and stakeholder-led holistic progressive biosecurity management along the value chain that integrate aspects of animal husbandry, welfare and One Health to reduce parasitic diseases, and antimicrobial use, and prevent the introduction of ticks into new areas.
- Raise awareness among farmers on the benefits of good husbandry and biosecurity practices for resilience to parasitic diseases, and benefits for consumer and environmental health.
- Raise awareness of acaricide resistance among livestock keepers, animal health workers, service providers and veterinary services, and provide trainings in responsible use of acaricides and integrated parasite management.
- Set up and strengthen national surveillance to monitor parasitic diseases and acaricide resistance in ticks.
- Strengthen regulatory bodies, legislations and policies to ensure the quality of acaricides along the supply chain.

The meeting advised FAO and the Tripartite organizations (FAO, WOAH, WHO) as follows:

- coordinate efforts towards effective management and control of resistant ticks on a global scale;
- update FAO (2004) guidelines for integrated control of ticks and management of acaricide resistance;
- establish a global Acaricide Resistance Management Network to exchange reference materials and data using quality-assured protocols and provide training on acaricide resistance testing;
- create an FAO Advisory Panel on Tick Resistance consisting of international experts to develop the best possible and sustainable tick control strategies;
- mobilize resources to implement integrated tick management approaches to mitigate the impact of resistance on farmers' livelihood.

Finally, the expert consultation provided the following recommendations to other stakeholders (e.g. research institutions, private sector, farmers, donors)

- develop research projects and collaborations to elucidate and characterize the mechanisms of resistance in different tick species against the current classes of acaricides used in livestock and identify molecular markers of resistance;
- participate in collaborative research projects to investigate innovative tick control methods, including the development of rapid pen-side diagnostics to detect resistance, new chemical entities with a different mode of action, vaccines, and alternative technologies;

- provide evidence of the efficacy of existing concepts of acaricide resistance management strategies (e.g. integrating acaricides and anti-tick vaccines, combinations, and rotation of acaricides with a different mode of action allowing translation into evidence-based recommendations and policies);
- set up a consortium like the Insecticide Resistance Action Committee (IRAC) between acaricide drug manufacturers, drug regulation governance and other experts to foster a harmonized approach to labelling and marketing acaricidal products;
- share local, regional, and national data on resistance in an open and accessible format to all stakeholders, including farmers using cellular phone-enabled application services.

Finally, concerted action by pharmaceutical producers, academic and research institutions, regulatory authorities, veterinary practitioners, and livestock farmers is required to address the increasing problem of acaricide resistance in livestock ticks.

Introduction

The Food and Agriculture Organization of the United Nations (FAO), in collaboration with the other Tripartite organizations (the World Organisation for Animal Health [WOAH] and the World Health Organization [WHO]), has been active for years in efforts towards controlling the emergence and spread of antimicrobial resistance in the livestock sector, aquaculture and crop production.

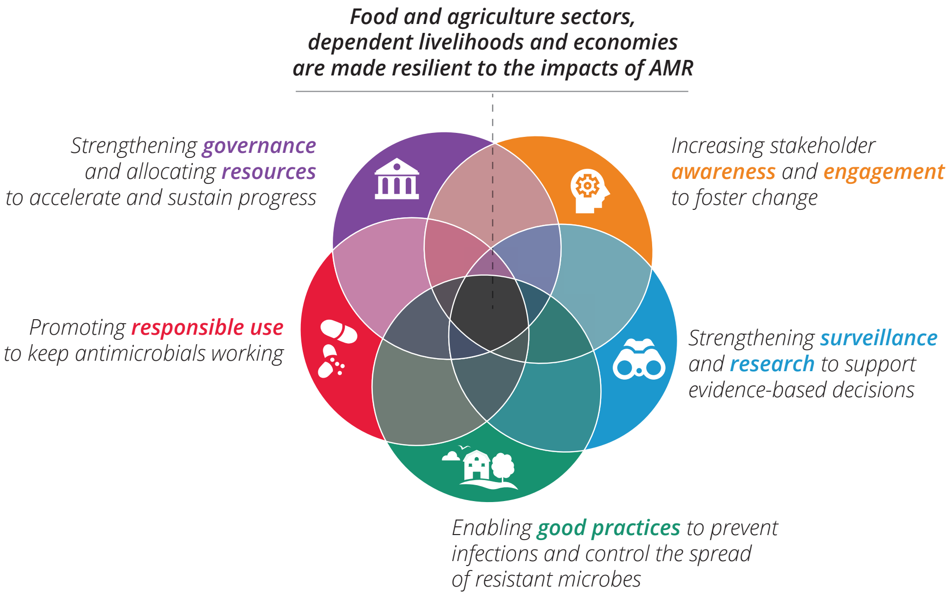
The year that FAO published the last guidelines on resistance management and integrated parasite control in ruminants (FAO, 2004) coincided with the publication of a special supplement in the journal *Parasitology*, volume 129, p.1–450, wherein Alan Bowman and Patricia Nuttall were able to bring together contributions from leading experts working in academia, government institutions, and the animal health industry sector to review advances and provide their views on the outstanding questions. It is interesting to revisit the chapters on the chemical control of ticks (George, Pound and Davey, 2004) and the industry point of view regarding tick control (Graf *et al.*, 2004). Progress over the past 17 years can be summarized as follows: chemical control of ticks on livestock remains heavily dependent on a limited number of acaricidal classes of compounds since no new categories have been introduced. In that same period, the number of scientific reports on acaricide resistance in ticks sharply increased, indicating greatly enhanced interest and importance of the matter.

The expert consultation was opened by Keith Sumption, the Chief Veterinary Officer at the Animal Production and Health Division of FAO, and the Director of the Joint FAO/WHO Centre for Zoonotic Diseases and Antimicrobial Resistance (CJWZ).

This expert consultation is a turning point in many ways and marks the initiation of an active role of FAO in the acaricide management of livestock ticks. A highlight of the past performance of a broad range of experts contributing to a set of practical field manuals that FAO produced to control ticks and tick-borne diseases of livestock in the tropics (FAO, 1984a, 1984b). The manuals introduced some very significant concepts, such as the use of **enzootic stability**. Parasites and parasitic diseases negatively affect the health and welfare of domestic animals and affect food security, and they place a heavy burden on livestock keepers. Moreover, some parasitic infections are also zoonotic. Therefore, just as we preserve antimicrobials for humans and animals, we need to maintain and manage these essential chemical compounds for animal production. Management and control of parasites often hinge on the use of chemicals and drugs such as acaricides. However, the resistance to those currently in use is spreading, making parasite management and control increasingly challenging.

FAO, WOAH and WHO work together under the Tripartite to promote the One Health approach. In 2020, FAO established a Joint FAO/WHO Centre for Zoonotic Diseases and Antimicrobial Resistance. It aims to coordinate/strengthen the FAO work on zoonotic diseases and AMR and foster collaborations with external partners to support global efforts to effectively address these threats at global, regional, and country levels through the One Health approach. FAO is re-engaging in the sustainable management of ticks and tick-borne diseases (TBD) in livestock challenged by the global emergence of resistance through the CJWZ.

Figure 1. From the FAO Action Plan on Antimicrobial Resistance 2021–2025



Source: FAO. 2021. *The FAO Action Plan on Antimicrobial Resistance 2021–2025*. Rome. https://doi.org/10.4060/cb5545en

Junxia Song referred to antimicrobial resistance, a major global threat of increasing human and animal health concerns. It also has implications for food safety and security and the economic well-being of millions of farming households. CJWZ supports the development of relevant policies, guidelines, strategies, and sustainable programmes to prevent and reduce the risk of AMR in food and in agricultural sectors. FAO recently launched the new FAO action plan on AMR 2021–2025.[1]

First, there is a need to reduce levels and slow the emergence and spread of resistance across the food chain and all food and agricultural sectors. Secondly, it is essential to preserve the ability to treat infections with effective and safe methods to sustain food and agriculture productions. The five key objectives are (1) increasing stakeholder awareness and engagement, (2) strengthening surveillance and awareness and research, (3) enabling good practices, (4) promoting responsible use, (5) strengthening governance, and allocating resources sustainably (Figure 1).

These five objectives, which are the pillars that support the efforts to mitigate antimicrobial resistance, are equally suitable to address similar issues related to resistance management of ticks and control of livestock and zoonotic TBDs.

A further initiative concerns the establishment of the AMR Multi-Stakeholder Partnership Platform, led by the Tripartite organizations (FAO, WHO and WOAH). The platform aims to bring together different voices across human, animal, plant, and environment interfaces. It will serve as an inclusive international platform at the forefront of strengthening a shared global vision on AMR and provide a venue for information-sharing, networking, and supporting the implementation of a global action plan and national action plans. The Tripartite organizations will launch the platform in 2022. The TBD expert group arising from this expert consultation could eventually contribute to a broader Parasite Resistance Action Group to be considered by the Steering Committee of this platform.

[1] Available from www.fao.org/3/cb5545en/cb5545en.pdf

Finally, FAO worked on tick-borne disease control for many years and coordinated multi-donor programmes in the 1980s and 1990s on controlling ticks and TBDs in eastern, central and south southern Africa. Research on TBDs and tick control in Kenya, United Republic of Tanzania and Uganda between 1967 and 1976 was very productive. It provided the basis for vaccination against East Coast fever and the in vitro cultivation of its causative agent *Theileria parva* (Uilenberg *et al.*, 1977; Radley, 1978). There is a need to update the guidelines on parasite resistance published by FAO in 2004.

BACKGROUND

Ticks and the diseases they transmit are widely distributed throughout the world, particularly in tropical and subtropical regions. It has been estimated that 80 percent of the world's cattle population is exposed to tick infestation. Although species of ticks and tick-borne diseases (TBD) differ among ecological regions, their impact on animal production is substantial wherever they occur (Jongejan and Uilenberg, 2004). Ticks, generally regarded as the ectoparasites that cause the greatest economic losses to livestock production in the world, adversely affect livestock hosts in several ways. Ticks contribute to anaemia by exsanguination; they damage hides and subject livestock to secondary infection; they cause toxicoses and paralysis by injecting their salivary secretions; and, most importantly, they transmit pathogens that cause diseases, many of which result in debility and death. Of the many tick-borne livestock diseases, four are particularly concerned: bovine anaplasmosis, bovine babesiosis, theileriosis, and heartwater. Chemical control, dipping or spraying infested cattle with acaricides is the primary method of dealing with the cattle tick problem. However, widespread exposure to acaricides, often at subeffective concentrations, has resulted in selecting resistant strains from tick populations. A situation has now been reached where cattle ticks in widely separated parts of the world have shown a capacity to develop resistance to most of the currently available chemical classes of acaricides.

SCOPE AND PURPOSE OF THE EXPERT CONSULTATION

Provide FAO with advice on the way forward regarding parasite resistance management. What is the current global status of acaricide resistance in ticks? Are the current diagnostic methods (FAO-recommended LPT) and molecular methods sufficient to monitor? What are the gaps in the distribution and detection of resistance in ticks? What are the current strategies to delay the emergence of resistance? Are co-formulated products the way forward concerning postponing the development of resistance?

The purpose is to contribute to sustainable management of ticks and TBD in livestock for enhanced food security leading to healthier livestock. Revised/improved policies on parasite resistance management are required to enhance farmers' livelihoods, improve nutrition, generate income, and promote equitable economic growth.

- Identify a pool of international experts on acaricide resistance who could contribute to the expert consultation and the subsequent development of guidelines for the management of parasite resistance.
- Organize multistakeholders' policy dialogues on challenges and options, promoting resistance management pathways and assisting governments in adopting new/revised policy frameworks.

The second day of the consultation focused on African animal trypanosomosis and drug resistance. Nine international speakers shared their experience, and a broader group of experts discussed the issues and formulated recommendations. The report of the second day of the consultation is available at https://doi.org/10.4060/cc2988en.

Current status of acaricide resistance in livestock ticks

Some of the major tick species on livestock worldwide are *Rhipicephalus microplus* (Canestrini, 1888), *Rhipicephalus annulatus* (Say, 1821), *Rhipicephalus decoloratus* (Koch, 1844), *Amblyomma variegatum* (Fabricius, 1794), *Amblyomma cajennense* (Fabricius, 1787), *Hyalomma anatolicum* (Koch, 1844) and *Haemaphysalis longicornis* (Neumann, 1901). H. longicornis was recently discovered on livestock in the United States of America in 2017 and has since then rapidly spread (ben Beard *et al.*, 2018; Raghavan *et al.*, 2019; Rainey *et al.*, 2018). Also, *Rhipicephalus appendiculatus* (Neumann, 1901), is an important local tick in east and southern Africa where is transmits East Coast fever (*Theileria parva* infection in cattle (Uilenberg *et al.*, 1977).

The **Asian blue tick or cattle tick, *Rhipicephalus microplus***, and the African blue tick, *Rhipicephalus decoloratus*, are among the most damaging tick species on cattle. Blue ticks have a one-host life cycle which they complete in three to four weeks on cattle resulting in heavy tick burdens. Two- and three-host ticks are much less exposed to acaricidal treatments and have, therefore, a lower probability of developing resistance. Ticks reduce life weight gain, devaluate hides and skin, and transmit potentially fatal cattle diseases.

Boophilus ticks were reassigned to the genus *Rhipicephalus* (farmers identify blue ticks on their cattle despite the name changes). Other ticks moved back to their old name like *Boophilus microplus*, now reinstated *Rhipicephalus australis* (Labruna *et al.*, 2009; Estrada-Peña *et al.*, 2012). The distribution of three major livestock ticks; *Rhipicephalus annulatus, Rhipicephalus microplus, and Rhipicephalus australis* is summarized by Burger, Shao and Barker (2014).

R. microplus ticks originated from South-East Asia and were introduced with cattle around 1900 from Asia into eastern and southern Africa. It has replaced the indigenous African blue tick over a vast area in East Africa (Barré and Uilenberg, 2010). *Rhipicephalus microplus* has been known for decades in United Republic of Tanzania (Lynen *et al.*, 2008).

In South Africa, the tick is now established in scattered areas along the southern and eastern coasts of the Western and Eastern Cape provinces and KwaZulu-Natal. It is also present in the coastal regions of Mozambique, Kenya and United Republic of Tanzania and the interior of Malawi, Zambia and Zimbabwe. The known distribution of *R. microplus* in sub-Saharan Africa published in 2005 has dramatically changed (Estrada-Peña *et al.*, 2006).

Importantly, *R. microplus* was introduced inadvertently with imported Brazilian cattle into West African countries, initially into Côte d'Ivoire, which was reported in 2007. The tick spread further into Angola, Benin, Burkina Faso, Cameroon, Mali, Nigeria and Togo (Silatsa *et al.*, 2019). Also, its presence in Kenya was only recently confirmed (Kanduma *et al.*, 2020). Recently, *R. microplus* invaded Uganda, where it replaced *B. decoloratus* in the south-eastern part of the country (Muhanguzi *et al.*, 2020).

HISTORICAL PERSPECTIVE, MODE OF ACTION AND RESISTANCE MECHANISMS

Tick control on livestock is heavily dependent upon acaricides, which has resulted in the development of resistance in one-host cattle ticks throughout vast areas in Latin America, sub-Saharan Africa, and parts of Asia. Resistance in cattle ticks has been reported against all acaricidal classes (organophosphates, synthetic pyrethroids, formamidines and macrocyclic lactones), leading to significant economic losses for cattle producers globally.

Classes of acaricides. The control of ticks infesting livestock almost entirely depends on commercial, synthetic acaricides. The current acaricides available on the market consist of five major classes of molecules.

Arsenicals

Arsenic dips were introduced in 1895 and used for about 40 years until resistance developed in ticks and more effective alternatives of acaricide products were developed. The first report of arsenic resistance in ticks was in 1936. Additionally, the environmental persistence of arsenic, which led to massive contamination of large areas of lands with lead arsenate residues, and the serious public health concern led to a complete ban.

Organochlorines

Organochlorines were introduced into the market to control tick infestations on cattle in the late 1930s (Graf *et al.*, 2004; dieldrin, toxaphene, lindane). Organochlorines offered high efficacy, a broad spectrum of action, and relatively less toxicity than arsenicals. However, the first report of resistance against organochlorines was in 1952 in Brazil (Graf *et al.*, 2004). Their propensities to accumulate in fat tissues led to the ban for tick control in 1962 (George, Pound and Davey, 2004).

Organophosphates

Organophosphates (OP) (chlorpyrifos, chlorfenvinphos, ethion, diazinon and coumaphos) were introduced in the mid-1950s. They are chemically unstable and non-persistent in the environment. The first documented case of OP resistance was in Australia in the mid-1960s. Due to their relatively high toxicity to livestock, many OPs have been withdrawn from the market (George, Pound and Davey, 2004).

Carbamates

The carbamates (carbaryl and propoxur) were introduced in 1954. Their popularity was based on a very low mammalian toxicity and a broad control spectrum. However, ticks resistant to organophosphates can exhibit cross-resistance to carbamates, and vice versa (George, Pound and Davey, 2004).

Formamidines

Formamidines were introduced for tick control in the mid-1970s. Among the formamidines, amitraz is the most effective for controlling ticks. Its toxicity to cattle and humans is minimal, and it is comparatively less persistent in the environment. However, the first amitraz resistance in ticks was reported in the early 1980s in Australia.

Pyrethroids

The current fourth generation of synthetic pyrethroids (SP) has exceptional insecticidal/acaricidal properties; they are photostable and have long residual effectiveness. They were introduced between 1975 and 1983, and include cypermethrin, cyhalothrin, bifenthrin, fenvalerate, alpha-cypermethrin, deltamethrin and flumethrin. Cypermethrin, deltamethrin, and cyhalothrin are the most used SP acaricides to control ticks. Resistance to SP was first documented in the late 1980s in Australia and Brazil (Rodriguez-Vivas, Jonsson and Bhushan, 2018).

Macrocyclic lactones

Macrocyclic lactones (ML) were introduced in the mid-1970s. They have acaricidal properties and belong to two groups: (i) the avermectins, which include ivermectin, abamectin, eprinomectin, doramectin; and (ii) the milbemycins, which includes moxidectin and milbemycin. Most of the avermectin-derived ML are on the market for tick control, but of the milbemycines, only moxidectin is available for tick control. ML have acaricidal efficacy at low doses and can be administered subcutaneously and pour-on formulations have also proven effective. The advantages of ML include prolonged residual activity and effectiveness in controlling a wide range of arthropods and nematodes. The first report of resistance to ivermectin and doramectin was in 2001 in Brazil and subsequently in Argentina, India, South Africa and Uruguay (Rodriguez-Vivas, Jonsson and Bhushan, 2018).

Growth regulators

In 1994, fluazuron became the first growth regulator on the acaricide market in Australia. Fluazuron adversely affects ticks on cattle exposed to this acaricide by reducing the reproductive capacity of engorged females and inhibiting the moulting of immature ticks (George, Pound and Davey, 2004). Fluazuron's residual effect can be long-lasting and can offer protection against *R. microplus* for up to 12 weeks. Fluazuron has some adverse effects on cattle in that its residue persists in fat and is excreted in milk. Cattle treated with fluazuron must be withheld from human consumption for six weeks. Another limitation of the use of fluazuron is the emergence of fluazuron-resistant ticks in Brazil and Columbia observed in 2014 (Rodriguez-Vivas, Jonsson and Bhushan, 2018).

Phenylpyrazoles

Fipronyl is the only phenylpyrazole compound used to control tick infestations on cattle and was introduced in the mid-1990s. Its application mode is as a pour-on to tick-infested cattle, and its acaricidal efficacy is over 99 percent, with its residual effect lasting for eight weeks (George, Pound and Davey, 2004). In 2007, the first fipronil-resistant *R. microplus* ticks were reported from Uruguay (Rodriguez-Vivas, Jonsson and Bhushan, 2018; Figure 4).

Mode of actions

The mode of action of the different classes of acaricides can be found on the website and app of the Insecticide Resistance Action Committee (IRAC) (Sparks *et al.*, 2021). Organophosphates are inhibitors of acetylcholineesterase (AChE), an essential enzyme of the nervous system. When inhibited, the neurotransmitter acetylcholine cannot be degraded, which leads to overstimulation of the nervous system and, ultimately, mortality of ticks. Pyrethroids are sodium channel modulators, and they cause changes in the permeability of the nerve cell membrane to ions, which causes nerve excitation. Formamidines (amitraz) exert toxicity on the octopamine receptor (Abbas *et al.*, 2014).

Resistance mechanisms

The basic mechanisms that underlie pesticide resistance are broadly classified into three categories:

- target-site mutations (target-site resistance);
- increased metabolic detoxification (metabolic resistance);
- reduced cuticular penetration (penetration resistance).

A combination of target-site modification and metabolic detoxification through cytochrome monooxygenases P450 has been attributed to resistance to amitraz. Moreover, target-site insensitivity (AChE) is associated with organophosphates and carbamates. In contrast, resistance to ML has been attributed to target-site insensitivity of the y-Aminobutyric acid (GABA) or glutamate-gated chloride ion channels. Metabolic resistance involves increased metabolic detoxification of acaricide mediated by the elevated production of detoxification enzymes. Metabolic resistance is mediated by three families of enzymes, namely esterases, monooxygenases (cytochrome P450s), and glutathione S-transferases (GSTs) (Guerrero, Lovis and Martins, 2012).

Toxicological bio-assays

The **larval packet test** (LPT) is a method for detecting resistance in cattle ticks initially recommended by FAO in its Plant Protection Bulletin published in 1971 (FAO, 1971) based on the original description by Stone and Haydock (1962). LPT has been further described in detail in the practical field manual of 1984 and discussed during an expert consultation held by FAO in Rome in 1977 (FAO, 1977). The LPT Protocol was updated in the guidelines published in 2004 and has been widely adopted as an FAO reference test for detecting resistance in ticks. LPT employs serial dilutions of acaricides impregnated into 7 x 10 cm Cytiva Whatman qualitative filter papers in triplicate. A mixture of olive oil and two parts trichloroethylene is used as the solvent. The control group consists of filter papers impregnated only with olive oil and trichloroethylene. Each filter paper is folded along the width to create a packet, sealed by bulldog clips. Other toxicological bio-assays include the **adult immersion test** (AIT), the **larval immersion test** (LIT), and the more recently introduced **larval tarsal test** (LTT; Lovis *et al.*, 2013).

Molecular assays

Monitoring acaricide resistance and understanding the underlying mechanisms are essential in developing resistance management and tick control strategies. Identification of single nucleotide polymorphisms in the acaricide-resistant associated genes of *R.microplus* has enabled the development of molecular markers for the detection of resistance. These include markers for mutations on target genes such as the sodium channel, AChE, carboxylesterase, β-adrenergic octopamine receptor, octopamine–tyramine. Molecular genotyping through molecular markers can detect the presence of resistance-associated genes in a tick population before it reaches high frequency. Molecular techniques include allele-specific polymerase chain reaction (PCR), target gene amplification, quantitative PCR assays, and transcriptomic analysis (Kumar, 2019).

COUNTRY REPORTS ON ACARICIDE-RESISTANT TICKS

The following country reports are based on the presentations made by the experts that were consulted at the meeting, but are not an accurate reflection. Only the key points are highlighted here and are supplemented with additional data from the literature. Strategies proposed by the presenters are discussed in the next chapter.

BRAZIL

Background: the economic impact of cattle ticks in Latin American is huge, with annual losses estimated at **USD 3 240 million** in Brazil, USD 573.61 million in Mexico, and approximately USD 300 million in Argentina, USD 45 million in Uruguay, and USD 22.5 million in Colombia.

The resistant ticks situation in Brazil was presented as a worst-case scenario, entitled "**The threat of the superticks**". In Brazil, tick control is based on six different classes of acaricides. Organophosphates, SP, amitraz, ML, fipronil and fluazuron. The last introduction was in 1994; after that, no new molecules were introduced. Tick control agents are administered in the form of dipping vats, pour-ons, sprays and injectables. Resistance has developed against all six classes of acaricides and will inevitably develop again against any novel class of acaricidal compounds. With its vast pastures with large herds of susceptible cattle in a tropical environment, Brazil has ideal conditions for cattle ticks. Resistance is highest in the primary cattle-producing states.

Selected data: at the Institute of Veterinary Research, "Desidério Finamor", more than 600 tick samples were tested between 2015 and 2019 for resistance to all six acaricidal classes. For this purpose, the AIT has its limitations, but this is the one that we have already been doing for the last 25 years (Drummond *et al.*, 1973). The test is used for all chemical classes and products wherein different acaricidal classes have been combined (e.g. cypermethrin and chlorpyrifos). The per-cent resistance varied between tick samples, ranging from 20–50 percent for organophosphates and fluazuron to 90 percent resistant to the SP (Klafke *et al.*, 2017). The highest multiple resistance levels occurred in the Rio Grande do Sul state, which has the highest cattle stocking rates. Since cattle producers appear to run out of options, some have moved to soybean production rather than cattle production in this area. Multiresistant ticks also occur elsewhere in Latin America, for instance, in countries like Colombia, Ecuador and Uruguay.

Novel rapid molecular diagnostics are needed because current bio-assays take six weeks. Since the cattle producer usually requires a quick answer in the resistance status of ticks, molecular methods can have a result within a week, and any life cycle stage of a tick can be used in molecular assays. Molecular tests are based on single nucleotide polymorphisms (SNPs) of target sites (e.g. sodium-channel or octopamine-receptor alterations which are linked to an increase in detoxification by esterases).

Molecular diagnostic tools offer the opportunity to detect resistance rapidly, which can be complemented with confirmatory bio-assays with larvae and adult ticks that are more resource- and time-consuming to generate. Synthetic pyrethroid resistance is one of the most prevalent and well-studied forms of resistance in arthropods, being linked with target-site alterations in the sodium ion channel gene. A novel molecular method to detect mutations in the para-sodium channel gene of *R. microplus* associated with acaricide resistance is based on quantitative PCR high-resolution melt (HRM) analysis. LPTs with discriminating doses and a modified lethal time analysis were performed to confirm resistance to permethrin, cypermethrin, deltamethrin, and flumethrin in laboratory strains. This technique could be adapted for high-throughput screening, detection, and discovery of allele-specific mutations in cattle tick populations (Klafke *et al.*, 2019).

Conclusions: molecular tests could be applied to integrated control programmes in other parts of the world where *R. microplus* is endemic and where similar SNPs have been identified associated with pyrethroid resistance.

MEXICO

Background: in Mexico, infestation of *Rhipicephalus microplus* results in losses in meat and milk, damage to hides and, finally, mortality due to tick-transmitted blood parasites, incurring an annual economic loss of USD 573.61 million. The intensive use of conventional acaricides and ML has led to a resistant tick population (Rodriguez-Vivas *et al.*, 2017). Amitraz and ivermectin resistance in *R. microplus* is common in Mexico, and the levels of ivermectins resistance in most *R. microplus* populations are relatively low. Despite the intensive use of flumethrin and coumaphos in Mexico, both acaricides can still control *R. microplus*.

Selected study data: the prevalence, resistance ratios, and factors associated with *R. microplus* populations resistant to amitraz, flumethrin, coumaphos, and ivermectin (IVM) were studied in Mexico. Field tick populations were collected from 54 farms in 15 different states of Mexico. The dose-response bioassays were carried out using the LIT (amitraz and IVM) and the modified LPT (flumethrin and coumaphos) for *R. microplus*.

The overall prevalence of cattle farms with *R. microplus* resistant to coumaphos, amitraz, flumethrin, and IVM were 25.9 percent, 46.2 percent, 31.5 percent and 68.5 percent, respectively. For coumaphos, 74.1 percent, 22.2 percent, and 3.7 percent were classified as susceptible, low resistant and high resistant, respectively. For amitraz, 53.7 percent, 24.1 percent, and 22.2 percent of phenotypes were susceptile, low resistant and high resistant, respectively. For flumethrin 68.5 percent, 14.8 percent, and 16.7 percent were susceptible, low resistant and high resistant, respectively. Finally, for ivermectine, 31.5 percent, 46.3 percent, and 22.2 percent were susceptible, low resistant and high resistant, respectively.

Amitraz and IVM resistance in *R. microplus* is frequent, but mainly at a low level in cattle farms of Mexico. Cattle farms without an acaricide rotation programme had a higher probability of developing *R. microplus* resistant to amitraz. Intensive use of conventional acaricides as well as ML has led to the development of resistant tick population (Rodriguez-Vivas *et al.*, 2017).

Conclusions: amitraz and ivermectin resistance in *R. microplus* is common in Mexico. The levels of ivermectin resistance in most of *R. microplus* populations are relatively low. Despite the intensive use of flumethrin and coumaphos in Mexico, both acaricides can still be used to control *R. microplus*. Cattle farms without acaricide rotation programme had a higher probability of developing *R. microplus* resistant to amitraz (Rodriguez-Vivas *et al.*, 2021).

UNITED STATES OF AMERICA

Background: the campaign in Texas to eradicate *R. annulatus* cattle ticks and bovine babesiosis started in 1906. Texas was declared cattle tick-free in 1943. Success was due to treatment with arsenic oxide and restriction of animal movements.

Selected study data: outbreaks of cattle ticks between 2012 and 2021 in the quarantine and free areas have been reported. These outbreaks have stimulated an ongoing project on integrated pest management of cattle fever ticks with the objective of determining variables that influence tick range, suitable tick habitats, the risk of tick-borne disease outbreaks and the potential for introducing invasive ticks. It is particularly relevant to develop strategies to control cattle fever ticks on wildlife, a refuge for cattle ticks. Native and wild ungulate species (red deer, white-tailed deer, wapiti and nilgai) are a complicating factor acting as mobile tick reservoirs in south Texas (Busch *et al.*, 2014; Lohmeyer *et al.*, 2018). The success of the early campaign was probably partly due to the lack of wildlife in the quarantine area.

An integrated strategy was developed including Bm86 vaccination for sustainable cattle fever tick eradiation in the United States of America for treatment of cattle fever ticks (Pérez de León *et al.*, 2012). This included the Bm86 vaccine which is highly efficacious against *R. annulatus* (98 percent), but only around 40 percent against *R. microplus*. Moreover, enhanced biosecurity measures have been implemented (Wang *et al.*, 2020). Cattle fever tick and bovine babesiosis are also part of a binational collaboration between United States of America- and Mexico-based scientists (Esteve-Gasent *et al.*, 2020).

The use of DNA-based real-time PCR assays to detect mutations within the voltage-sensitive sodium channel involved in permethrin resistance has been recently developed. These assays can be completed within days of receiving field-collected ticks providing timely, valuable information to programme managers.

Conclusions: a pilot tick eradication programme is ongoing using microsatellite marker analysis of pyrethroid-resistant tick populations delivered evidence that separate incursions of resistant ticks had entered Texas independently (Thomas *et al.*, 2019).

BENIN AND BURKINA FASO

Background: in West Africa, most people depend on cattle farming and subsistence agriculture. The presence of ticks on cattle is a major problem faced by smallholder farmers. National and regional tick control programmes could assist these rural communities in protecting their livelihoods against ticks and TBD, but only if they consider the targeted herders and their perception on cattle management and tick control.

Selected study data: the socioeconomic characteristics of Beninese cattle farmers, their perception of tick burden, and their common tick control strategies were recently documented. Different tick species and their seasonality are well understood by cattle herders. For tick control, many still use manual tick removal, especially in the north of the country. The high cost of acaricides limits the use of acaricides in livestock breeding in Benin. While aiming to increase the meat or milk production of their animals, stockbreeders who can afford it sometimes turn to an abusive use of acaricides, which might in time lead to an increase in tick resistance (Adehan *et al.*, 2016).

Transhumance, a main ancestral animal production strategy of the West African countries, can favour the spread of vectors and vector-borne diseases within and/or across countries. Transhumance has been implicated in such spread, as have related TBDs. Using a questionnaire survey and statistical modelling, this study explores the perception of herders about ticks and TBD in cattle, their practices in tick control and the social groups involved in cattle farming in eastern Burkina

Faso (46 random herds) and in the northern Benin (44 random herds). Herders in Benin use less acaricides in their treatment calendar compared with those in Burkina Faso. Transhumant pastoralists plan more acaricide treatment and have more cows with lost teats (i.e. tick damage) than the sedentary ones. Amitraz appears to be the main acaricide used for tick control (68 percent) but its use is inappropriate, and its source is frequently the unregulated market. All these findings can induce acaricide resistance, especially as the inefficacy of amitraz against *R. microplus* has already been reported in previous studies. Such results would help elaborate suitable strategies of control and prevention of ticks and TBD in Burkina Faso and Benin (Zannou *et al.*, 2021).

In a study in Burkina Faso, 73 percent of farmers (n=60) used SP and amitraz in sprays, others used hand picking, or plastered cattle with dung or engine oil, and several others used crop pesticides (Adakal *et al.*, 2013). Treatment failures appeared to be linked to SP. More recently, in Burkina Faso and Benin, 68 percent of farmers used amitraz, 18 percent SP and 4 percent fipronil; 55 percent used a brush, 23 percent used a spray, 16 percent used a pour-on and 6 percent removed ticks by hand. Farmers purchase acaricides from local markets or local veterinary pharmacies.

Resistance appears to be limited to *R. microplus*, whereas *Rhipicephalus geigyi* and *Amblyomma variegatum* were susceptible to deltamethrin and cypermethrin (Ouedraogo *et al.*, 2021).

Conclusions: Resistance is widespread in Burkina Faso and also in Benin, where resistance varied according to the acaricidal classes (Adehan *et al.*, 2016).

UGANDA

Background: The livestock industry contributes 19 percent towards Uganda's gross domestic product with more than 70 percent of Ugandans employed in agriculture. The increase in the number of farms that are crossbreeding exotic cattle with indigenous breeds has led to the development of a population of crossbred animals more susceptible to ticks and TBDs. Inappropriate husbandry practices and acaricide application practices are also factors driving development of acaricide resistance in ticks (Vudriko *et al.*, 2018).

Selected study data: a cross-sectional study with tick samples from 54 purposively selected farms demonstrated that 90 percent of R. appendiculatus and *R. decoloratus* were resistant to SP with 55.2 percent being multi-acaricide-resistant as determined by the LPT ticks (Vudriko *et al.*, 2016). From 2019 to 2020, a national tick acaricide resistance survey was carried out in 357 farms. *R. decoloratus* (n=90) and *R. appendiculatus* (n=86) were tested in addition to *Rhipicephalus evertsi* and *Hyalomma* species. Both *R. decoloratus* and R. appendiculatus were highly resistant, whereas the other two tick species were susceptible.

The prevalence of multi-acaricide resistance in cattle ticks, particularly *R. decoloratus* and R. appendiculatus, to three different classes of acaricides (SP, OP and amitraz) has a major impact. Farmers have indicated that ticks and TBD are the major cause of losses in production, in particular East Coast fever (*Theileria parva*). Farmers are left with limited options but to treat all exotic crosses with antibiotics to prevent transmission of tick-borne pathogens (Byaruhanga *et al.*, 2020). This is clearly a driver for the development of antimicrobial resistance. In one district, there was a shift from the use of SP, OP, combination products and amitraz to the use of agrochemicals and injections with ML.

Conclusions: in the absence of policies and strategies against ticks and TBD, multiacaricide resistance can emerge and spread rapidly to cause undesired consequences to animal health, livelihoods, public health, and the environment. Multiacaricide resistance is a potential driver for antimicrobial resistance and anthelminthic resistance. There is a need to urgently develop policies, strategies for tick and TBD control and commit resources for acaricide resistance management in ticks.

SOUTH AFRICA

Background: the widely used methods for applying tick control to cattle in South Africa are dip-tanks, spray races, hand-spraying, pour-ons, or hand-dressing. A broad range of acaricides is used including organophosphates, carbamates, formamidines, SP and ML to control ticks. Cattle ticks, particularly *R. microplus* and *R. decoloratus*, have developed resistance against a range of these acaricides and this is a constraint to livestock farming. Incorrect concentration and application methods are zero factors that accelerate the development of acaricide resistance. Cattle farmers in South Africa manage acaricide resistance by using communal farmer's knowledge, attitudes and practices on ticks and TBDs affecting cattle, tick control methods and their knowledge on acaricide resistance.

Selected study data: questionnaires were randomly administered to cattle farmers in Sinqu and Elundini communities in the Eastern Cape Province, South Africa. About 59 percent of the farmers had no knowledge of the effects of TBD on cattle production, and 78 percent of respondents reported that ticks are the major challenge to cattle farming. Pour-ons (61 percent) were the most used acaricidal treatment system with fortnightly (40 percent) treatment frequency during the summer season and during the winter season (31 percent). Pyrethroids (73 percent) were the most widely used acaricide compounds to control ticks, and about 65 percent of respondents were perceived to have no knowledge of the use of ethnoveterinary medicines to control ticks. Inefficacy of acaricide-treated (44 percent) and undipped animals (42 percent) were regarded as the major contributing factors to the increased tick population and acaricide resistance. About 85 percent of respondents were perceived as not practising acaricide rotation and 88 percent of the respondents had no knowledge of the acaricide resistance. Within the context of this study, ticks and tick-associated diseases are perceived by these farmers as the most important disease problem their cattle face (Yawa *et al.*, 2020).

With respect to *R. microplus*, there are several studies in east and southern Africa wherein the progressive displacement of the local African blue tick *R. decoloratus* by the invasive Asian blue tick has been documented (Lynen *et al.*, 2008; Nyangiwe, Harrison and Horak, 2013; Nyangiwe *et al.*, 2017; Kanduma *et al.*, 2020; Muhanguzi *et al.*, 2020). *R. microplus* has been reported to develop resistance to the major chemical classes of acaricides currently in use. In the Mnisi community in the Mpumalanga region, the adaptive potential of *R. microplus* for developing acaricide resistance was studied. The level of acaricide resistance was evaluated using SNPs in genes that contribute to acaricide insensitivity.

A high prevalence of alleles attributed to resistance against formamidines (amitraz) in the octopamine–tyramine receptor (frequency of 0.55) and pyrethroids in the carboxylesterase (frequency of 0.81) genes were observed. From these allele frequencies it appears that formamidine resistance in the Mnisi community is on the rise, as the *R. microplus* population is acquiring or generating these resistance alleles.

Apart from rearing multiresistant ticks to commonly used acaricides in this community, these ticks may pose future problems in surrounding areas (Robbertse *et al.*, 2016).

Conclusions: In further unpublished studies there was a poor correlation between SNP in the octopamine–tyramine receptor and resistance to amitraz in field ticks. Moreover, experimental exposure of ticks to sublethal concentrations of amitraz did not change this percentage. Other mechanisms such as detoxification must play a role in the development of resistance to amitraz. Importantly, a novel dipstick assay was developed to correctly measure the amitraz concentration in dip-tanks.

CHINA

Background: Ticks are widely distributed in China, with more than 120 species reported throughout its provinces. At present, China mainly relies on acaricides to control ticks. Organophosphates (diazinon) and SP are the most widely available acaricides in the market. There are few studies on the resistance of ticks to acaricides in China.

Selected study data: Lanzhou Veterinary Research Institute has carried out the following (unpublished) work. TaqMan probes were designed to screen for resistance gene markers. Results were compared with the resistance detection method (LPT) recommended by FAO. Real-time quantitative PCR testing was used to screen 1 300 ticks from 15 provinces in China, including Hunan, Gansu, Zhejiang, Qinghai, Xinjiang Uyghur Autonomous Region, Ningxia Hui Autonomous Region, Shanxi, Guangxi, Guizhou and Fujian. The sodium channel resistance gene rate was 87.7 percent by real-time fluorescence quantitative PCR, and 47 percent by standard PCR.

Moreover, more than 700 ticks were collected from six strains of *R. microplus* in Hunan, Guizhou, Guangxi, Fujian and Yunnan provinces. The acaricide resistance level of pyrethroid in these batches was measured by the LPT. SNPs were also examined. The results showed no mutation in the Hunan strain, four sodium channel mutation genes in the Guizhou and Fujian strains, three sodium channel genes in the Guangxi strain, and two sodium channel genes in the Yunnan strain. At the same time, acaricides commonly used in the Chinese market were selected to detect multidrug resistance to the tick strains collected from Guizhou and Fujian. The main chosen drugs were OP (diazinon, dichlorvos), ML (ivermectin), amitraz and fipronil.

Conclusions: resistance to different classes of acaricides was detected and varied according to the strain of the ticks.

INDIA

Background: dairy production in India consists of an organized sector wherein animals are kept in good condition, stall-fed with proper veterinary care including regular use of acaricides. The unorganized sector consists of small and marginal farmers with cattle kept under unhygienic conditions, no proper veterinary care and erratic use of acaricides. Most small holder farmers own on average two to four animals. In organized dairy farms, ticks are not able to survive indoors, whereas in poorly organized farms, ticks can develop and thrive in cracks and crevices indoors. This sector is producing 60 percent of the total milk production.

Acaricides, predominantly deltamethrin, cypermethrin, amitraz and ivermectin are used indiscriminately. There is no uniformity in usage and selection is based on what is available on the local market. Also, ease of administration is a factor in favour of ivermectin usage.

Selected study data: the AIT and LPT were used in addition to biochemical and molecular assays. Discriminating concentrations (2 x LC50) have been determined for most acaricides in India. Resistance studies started in 2011 and most studies have used the discriminating dose in the toxicological bio-assays. Distribution of resistant ticks varies between different states of India, possibly also due to non-standardized sampling (Singh *et al.*, 2014).

Monitoring of acaricide resistance in field ticks and use of suitable management practices are essential for controlling tick populations infesting livestock. The acaricide resistance status in *R. microplus* ticks infesting cattle and buffaloes in five districts located in the eastern Indian state of Bihar were characterized using three datasets (AIT, biochemical assays and gene sequences). AIT was adopted using seven field isolates and their resistance factor (RF) was determined. Six isolates were found to be resistant to both deltamethrin and diazinon and all except one isolate were resistant to cypermethrin. To understand the possible mode of resistance development, targeted enzymes and gene sequences of the para-sodium channel and AChE were analysed. Four novel amino acid substitutions in the AChE2 gene of field isolates and in OP-resistant laboratory reference IVRI-III tick colony were identified. Resistance in pyrethroids appears to be linked to sodium channel mutations, and point mutations in AChE point towards resistance in OP compounds. Amitraz and ivermectin resistance mechanisms are not yet fully elucidated. Comparative detoxifying enzyme profiles revealed a significant correlation between increased activity of esterases and SP resistance (Ghosh *et al.*, 2015).

The intensive usage of chemical acaricides for the control of cattle ticks has resulted in the development and establishment of multiacaricide-resistant populations. Fipronil, a phenylpyrazole insecticide, is currently marketed in India for the management of this important veterinary tick species. Indian isolates of *R. microplus* were tested for multiacaricide resistance, as well as for their susceptibility to fipronil. Twenty-five field isolates from five agroclimatic zones of the country were collected and tested using the AIT and the LPT. Sixteen isolates with RFs in the range of 1.56–10.9 were detected using the LPT, whereas only 11 isolates with RFs ranging from 1.05 to 4.1 were detected using the AIT. A significant variation of RFs between both tests was found, which raises doubts about the suitability of larvae-based assays in the screening of fipronil resistance. The data indicated possible cross-resistance between groups of acaricides in fipronil-resistant tick populations (Shakya *et al.*, 2020).

Conclusions: mitigation strategies include shed management to eliminate tick hiding places and strategic use of acaricides. Also, manual removal of ticks and predation by chickens are practised. No national resistance monitoring is in place and the market for acaricides is highly unregulated (Kumar, Sharma and Ghosh, 2020).

AUSTRALIA

Background: the cattle tick found in Australia, formerly referred to as *R.(Boophilus)* microplus, has been reclassified and is now referred to as R. australis (Labruna *et al.*, 2009; Estrada-Peña *et al.*, 2012). It is one of the most economically important diseases present in cattle in Australia. If left unchecked, cattle tick can significantly reduce cattle live-weight gain and milk production. It is responsible for transmitting three blood-borne tick fever organisms, Babesia bovis, Babesia bigemina and Anaplasma marginale, which cause "tick fever". Tick fever results in sickness and mortality in susceptible cattle. The estimated annual costs are around USD 160 million for treatment and lost productivity. Cattle ticks pose a significant threat to animal health and production throughout the tick-infested zones of Queensland, the Northern Territory and in the Kimberley region of western Australia. Periodic outbreaks also occur in the tick-free zones of these states, as well as in northern New South Wales.

The distribution of cattle ticks in Australia is largely controlled by regulation through a zone across northern Australia and is separated from the tick-free zone in southern Australia by the tick line, which is a series of legislated movement controls managed by quarantine and regulated eradication campaigns. Growth regulators (fluazuron), amitraz and ML (moxidectin) are widely used, the former also for treatment of cattle prior to movement from the tick-infested to the tick-free zone.

A survey of acaricide resistance survey was completed in 2006, wherein 290 producers were contacted and only 159 tick samples were obtained and 133 tick samples tested for resistance to OP, SP, amitraz, ML and fluazuron. Most producers used amitraz. Eighty percent resistance in OP was found even after more than 10 years without usage. SP resistance was around 50 percent and less than 10 percent was resistant to amitraz.

Amitraz is an important product for cattle tick control worldwide. It is quite affordable and it has a rapid knock-down effect. It binds with and activates adrenergic neuro-receptors and it inhibits the action of monoamine oxidases. The proposed mechanisms include genetic target-site insensitivity in two G protein-coupled receptors, the beta-adrenergic octopamine receptor and the octopamine–tyramine receptor, increased expression or activity of monoamine oxidases and increased expression or activity of the ATP-binding cassette transporter.

Conclusions: with respect to amitraz, four resistance mechanisms have been proposed, each of which is supported by evidence but none of which has been definitively confirmed as the cause of resistance in the field (Jonsson *et al.*, 2018).

Strategies for livestock tick control in a world of acaricide resistance

Several strategies discussed at the expert consultation are presented here. However, to provide a comprehensive overview of the entire field, including Latin America, sub-Saharan Africa and Asia, further consultations are required with all stakeholders, including existing networks on ticks and TBD (Nchu *et al.*, 2020).

Tick control is complex and depends on many management practices, such as agricultural land use, cattle stocking rates, host breed resistance to ticks, tick population dynamics, and the acaricidal application interval. Despite resistance problems, acaricides remain the best option to control ticks. However, the number of acaricidal classes is limited. Hence, there is a need to sustain the use of existing acaricidal classes. Fortunately, the agrochemical industry's outlook for novel acaricides and insecticides is intense (Jeschke, 2021).

Acaricide management of ticks on livestock is divided into three categories:

Intensive tick control: implies frequent applications of acaricides throughout the year to keep animals free of ticks and prevent pathogen transmission. The economic benefits of eradication of ticks through intensive tick control are enormous. A successful example is the eradication campaign in Texas. However, continuing surveillance is required due to incursions from Mexico, refuge of ticks on wildlife is a concern, and cooperation of farmers is crucial (Walker, 2011).

Strategic tick control: aims to reduce tick populations and transmission of pathogens; the timing of acaricide application is based on the seasonal occurrence of ticks with a variable number of applications. Acaricides are applied at strategic times of the year to control seasonal tick abundance peaks. It is aimed mainly at adult ticks to decrease numbers to levels at which economic damage is less than the cost of control. Other strategic tick control includes rotation of acaricidal classes and combining acaricidal classes into the same product.

The rotation strategy, which implies different alternating groups of pesticides with no cross-resistance, has not been implemented significantly. Farmers choose between classes of acaricides available on the market rather than follow any predetermined strategy. The use of mixtures is another promising approach. The belief is that rotation is no longer possible when combined acaricidal classes have delayed exploring this opportunity for the livestock sector. There is much to learn about how mixtures are exploited to delay insecticide resistance in mosquito vector control programmes.

The **Insecticide Resistance Action Committee** (IRAC) advocates using mixtures as follows: the probability of resistance developing simultaneously in two different classes of active ingredients will be extremely rare. There should be no evidence of cross-resistance between the mixture partners and preferably, they should act synergistically. For instance, a mixture of amitraz with cypermethrin and piperonylbutoxide led to high mortality of the resistant ticks in both in vitro and in vivo conditions. Combinations of different groups have been employed for many years in several countries to control ticks and insects. In South America, control of Triatoma infestans, the primary vector of Trypanosoma cruzi, was enhanced by a combination of deltamethrin with amitraz amitraz (Dadé *et al.*, 2020).

Co-formulating deltamethrin with amitraz could be used to control both ticks and tsetse in sub-Saharan Africa. This approach will solve a problem identified in Uganda where a conflict of interest between amidines over more expensive pyrethroids has been documented (Bardosh, Waiswa and Welburn, 2013).

Threshold tick control: aims to control ticks when they exceed a predefined, economically damaging number of ticks. A study in Mexico reported that the number of macrocyclic lactone applications per year is associated with the development of ivermectin-resistant populations. There is a significant relationship between the frequent application of acaricides and the development of resistance. Acaricidal applications can be opportunistic, and only those animals with tick burdens considered above the economic threshold could be treated. This should reduce both treatment costs and delay the development of acaricide resistance.

Strategies in Latin America

An intensive production system with a high cattle stocking rate requiring high acaricide levels is not sustainable. Ultimately, new molecules with a different mode of action are needed, which should be used wisely. In terms of integrated control strategies, the rational use of acaricides, anti-tick vaccines, bio-acaricides, biological control methods and host resistance must be considered.

Strategies in India

Livestock in general and the dairy sector, in particular, plays a vital role in the Indian economy and the socioeconomic development of millions of people. R.microplus is the most prevalent cattle tick in various agroclimatic zones of India. Due to the inadvertent and indiscriminate use of chemicals to kill ticks, the field tick population has developed resistance to almost all chemicals used to manage them. The current status of resistance in ticks, the possible mechanisms of resistance operating in the tick population, factors contributing to the development of resistance, and the managemental strategies have recently been thoroughly reviewed elsewhere (Kumar, Sharma and Ghosh, 2020).

Strategies in sub-Saharan Africa

Cattle have been present in Africa for more than a thousand years and until the twentieth century survived without specific control measures against ticks and TBD. It is now known that cattle can develop resistance to ticks, with the level of resistance developing in indigenous breeds being much higher than that in European Bos taurus cattle. Indigenous Zebu and Sanga cattle will also acquire immunity to the indigenous TBD if exposed to them at an early age, at a much higher level of immunity than imported Zebu or European Bos taurus can acquire. A situation in which cattle develop immunity to TBD through natural exposure as calves is called endemic stability. Most losses due to TBD occur in endemically unstable conditions, where there are insufficient infected ticks to ensure that all calves receive a challenge. TBD also cause losses if they are introduced, together with their vectors, to new regions and spread through susceptible livestock populations or if susceptible animals, especially exotic breeds, are moved to endemic areas.

Compulsory dipping has now been abolished throughout most of sub-Saharan Africa. However, most farmers continue to treat cattle at regular intervals with acaricides. Tick resistance in various cattle breeds has been compared in several countries in sub-Saharan Africa. These comparisons have demonstrated that Sanga and Zebu cattle are considerably more resistant to the commonly occurring tick species than European B. taurus cattle are and that crossbred cattle show intermediate resistance. Farmers in the traditional sector almost entirely rely on the enhanced genetic resistance of their animals to ticks and TBD in sub-Saharan Africa. This also implies that upgrading their stock with more productive genetic traits is severely limited by ticks and associated diseases.

Acaricide resistance is a significant concern in one-host cattle ticks. Two- and three-host ticks are much less exposed to acaricidal treatments and have a lower probability of developing resistance but are important for disease transmission. Acaricide resistance management is a global problem, and experience elsewhere, particularly in Latin America and India, could also help control African livestock ticks.

Advisory Panel on Tick Resistance

The creation of an FAO **Advisory Panel on Tick Resistance** will ensure continued and up-to-date advice from the key stakeholders to collectively create sustainable strategies for the management of resistance in livestock ticks. The panel terms of reference are similar to the scope of the FAO Action Plan on Antimicrobial Resistance 2021-2025.

Furthermore, the panel could transition and contribute to an **Action Group on Parasite Resistance**, encompassing ectoparasites, blood parasites (trypanosomes) and endoparasites (helminth infections), to be considered by the Steering Committee of the AMR Multi-Stakeholder Partnership Platform.

There are two main goals:
(1). **Reduce acaricide resistance prevalence and slow the emergence and spread of resistant livestock ticks.**
(2). **Preserve the ability to treat livestock with effective and safe acaricides to sustain food and agriculture production.**

This is how the five objectives laid down in the FAO Action Plan on Antimicrobial Resistance 2021-2025 translate into the sustainable management of livestock ticks:

(1). Increasing stakeholder awareness and engagement:
- **Develop training courses/educational material/webinars on acaricide resistance management of livestock ticks.**

(2). Strengthening surveillance and research:
- **Develop and implement rapid tests (toxicological bio-assays, biochemical assays, and molecular PCR-based assays) for detecting resistance in ticks for data collection to support evidence-based decisions.**
- **Collate a comprehensive review of the acaricide resistance status of cattle ticks with an update on its current geographical distribution.**

(3). Enabling good practices:
- **Promote the use of suitable containers for acaricides to enable proper measurement of concentrations and safe handling.**
- **Promote good antibiotics practices in conjunction with acaricidal treatments to block transmission of tick-borne disease pathogens (*Ehrlichia ruminantium* [heartwater]).**

(4). Promoting responsible use:
- **Provide guidelines for responsible use of acaricides and management of resistant ticks on livestock including governance and regulation of the production and distribution of acaricides.**

(5). Strengthening governance and allocating resources sustainably:

- **Coordinate research into novel combinations of acaricides which could mitigate resistance in selected livestock production areas.**
- **Integrate those with non-acaricidal methods into sustainable tick control strategies**.

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Glossary

Acaricide resistance has been defined as:

A specific heritable trait in a population of ticks selected as a result of the population's contact with an acaricide, which results in a significant increase in the percentage of the population that survives after exposure to a given concentration of that acaricide (Rodriguez-Vivas, Jonsson and Bhushan, 2018).

Intensive tick control: implies frequent applications of acaricides throughout the year to keep animals free of ticks and prevent pathogen transmission (Pegram, Hargreaves and Berkvens, 1995).

Strategic tick control: aims to reduce tick populations and transmission of pathogens. The timing of acaricide application is based on ecological information on the seasonal numbers of ticks, and the frequency of applications will vary during the year (Pegram, Hargreaves and Berkvens, 1995).

Threshold tick control: aims to control ticks when they exceed a predefined, economically damaging number of ticks (Pegram, Hargreaves and Berkvens, 1995).

Endemic stability: a state of a host-tick-pathogen interaction in which there is a high level of challenge of calves by infected ticks, the absence of clinical disease in calves despite infection, and a high level of immunity in adult cattle with a consequent low incidence of clinical disease. Endemic stability is an excellent epidemiological concept for bovine babesiosis (Jonsson *et al.*, 2012).

ANNEX 1
Meeting agenda

DAY 1 | **9 November 2021**

CURRENT STATUS AND MANAGEMENT OF ACARICIDE RESISTANCE IN LIVESTOCK TICKS

Moderator: Frans Jongejan
University of Pretoria – Faculty of Veterinary Science, South Africa

SESSION 1

14.00–14.05	**Opening remarks** Keith Sumption Chief Veterinary Officer Food and Agriculture Organization of the United Nations (FAO)
14.05–14.20	**The antimicrobial resistance programme at FAO** Junxia Song Senior Animal Health Officer Food and Agriculture Organization of the United Nations (FAO)
14.20–14.40	**Keynote address: The threat of the superticks** Guilherme M. Klafke Rio Grande do Sul State Secretariat of Agriculture Rio Grande do Sul, Brazil
14.40–14.55	**Multiacaricide-resistant cattle ticks emerged in Uganda** Patrick Vudriko Makerere University, Uganda
14.55–15.10	***Rhipicephalus microplus* resistance threats to livestock in India** Srikanta Ghosh Indian Veterinary Research Institute Izatnagar, India
15.10–15.40	**Open discussion: Diagnosis and monitoring of acaricide resistance in ticks**

SESSION 2

15.40–15.55	**Reflecting upon management policies for resistant cattle ticks in Australia** Nick Jonsson University of Glasgow, United Kingdom of Great Britain and Northern Ireland
15.55–16.10	**Integrated eradication strategies for cattle fever ticks in the United States of America** Adalberto Á. Pérez de León United States Department of Agriculture (USDA), United States of America
16.10–16.25	**Integrated control of *Rhipicephalus microplus* ticks resistant to conventional acaricides and ivermectin in Mexico** Roger Ivan Rodriguez-Vivas Universidad Autónoma de Yucatan, Mexico
16.25–16.40	**West African livestock system facing acaricide resistance of ticks** Abel S. Biguezoton *Centre international de recherche-développement sur l'elevage en zone subhumide (CIRDES), Burkina Faso*
16.40–16.55	**Control of ticks resistant to acaricides in East and Southern Africa** Nkululeko Nyangiwe Dohne Agricultural Research Institute, Eastern Cape, South Africa
16.55–17.10	**Insecticide resistance management: a private sector perspective** Juergen Langewald Chair: Insecticide Resistance Action Committee (IRAC), Germany
17.10–17.25	**Insights gained from the genetic development of acaricide resistance in cattle ticks: from genes to diagnostics and the next generation of acaricides** Christine Maritz-Olivier University of Pretoria, South Africa
17.25–18.00	**Conclusions and recommendations (acaricide resistance)** Moderators: Junxia Song (FAO/AMR) and Frans Jongejan (University of Pretoria)

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Availability: November 2022

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ISBN 978-92-5-137216-6

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CC2981EN/1/11.22