Chapter

Integrated Management of the Cattle Tick *Rhipicephalus (Boophilus) microplus* (Acari: Ixodidae) and the Acaricide Resistance Mitigation

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Abstract

Resistance to insecticides is one of the major obstacles to the control of agricultural pests, as well as species important to human and veterinary health. The World Health Organization has called insecticide resistance "the great little obstacle against vector-borne diseases". *Rhipicephalus (Boophilus) microplus* is one of the most important vector, transmitting diseases to cattle such as anaplasmosis and babesiosis. These diseases cause great economic losses that significantly increased because of the appearance of tick populations resistant to acaricides, as a result of the intensive use of pesticides. Resistance to ixodicides in Latin America is a growing problem, since control of disease-transmitting ticks, depends heavily on the use of pesticides. In Mexico, the resistance of *R. microplus* to organophosphate compounds, pyrethroids, and recently amidines, has been detected in some areas, affected by multiple acaricide resistance to the three families of ixodicides. The cattle tick *R. microplus* in addition to the great ecological impact represents the most expensive pest for livestock in Mexico, since the producers are directly affected by this tick, due to the decrease in the production of meat, milk and damage to the skin, as well as the indirect damage, such as the transmission of diseases, including Anaplasmosis and Babesiosis, which, in turn, represents a serious limitation for the introduction of specialized cattle in endemic areas. Therefore, the use of integrated management programs is a mandatory issue that should be implemented in all those areas affected by this parasite.

Keywords: ticks, *R. microplus*, tick control, tick vaccines, insecticides, Acaricide resistance

1. Introduction

Parasitic diseases are a global problem for health and animal production performance due to endoparasites or ectoparasites, Among ectoparasites (ticks, mites, flies, fleas mosquitoes etc.), ticks have adapted to most of the terrestrial niches on the planet and have specialized in feeding on the blood of mammals, birds and reptiles around the world [1–3]. The evolutionary adaptation of ticks to hematophagy, is the major reason of the great economic losses caused by this group of parasites, however, the greatest impact of tick infestations to human and animal health is also related with the tick borne diseases.

Ticks are considered responsible for more than 100,000 cases of human diseases, and are the most important vectors of disease-causing pathogens in wild and domestic animals. Globally, they are the second most important disease vectors in humans only after the mosquitoes [4, 5], however they are considered to be the most important vector of pathogens in North America [6].

The families Argasidae and Ixodidae are two groups of thelmophagous ticks of great importance for human and animal health, since they act as reservoirs of a lot of pathogens including parasitic protozoos (*Babesia spp* and *Theileria spp*.), bacteria (*Rickettsia spp*., *Ehrlichia spp* and *Anaplasma spp*), viruses (Nairovirus, Flavivirus and Asfavirus) and nematodes (*Acanthocheilonema*) [5].

Ticks belong to the group of ectoparasites that cause important economic losses in the cattle industry in tropical and subtropical ecosystems all over the world. Specifically, *R. microplus* causes direct damage due to the action of bites [7] and indirect damage caused by the transmission of three etiological agents: *Babesia bovis*, *Babesia bigemina* and *Anaplasma marginale* [8]. In the US prior to the eradication of *R. microplus* and *R. annulatus*, indirect economic losses from babesiosis were estimated at $ 130.5 US million dollars (which today would be three US billion dollars). If ticks had not been eradicated from the US, the livestock industry's annual losses due to ticks would be approximately one billion US dollars [9, 10]. Currently, the Texas Animal Health Commission (TAHC) has expanded the preventive quarantine zone in South Texas, because of the presence of resistant ticks on livestock and wildlife in 139 grassland areas [11]. The aim of this review is to contribute to the discussion of the cattle tick issues, as well as to provide a reference, for all those interested in the current problem of acaricide resistance, the importance of vaccine development and the perspectives of tick genomic research in Mexico.

2. *Rhipicephalus (Boophilus) microplus* life cycle

Rhipicephalus (Boophilus) microplus, is an important endemic tick specie causing great loses and damages to livestock production in tropical and subtropical regions [12]. It is a one-host telmophagous ectoparasite, showing a parasitic and a free living stage and four different evolutionary ontological stages: Egg, larvae, nymph and the adult engorged female (**Figure 1**).

Bovine cattle is parasitized by *R. microplus* as a preferred host, however, it can sporadically infest horses, sheep and goats. Its life cycle is divided in two phases: the parasitic and the non-parasitic free living stages, as well as four ontological stages: egg, larva, nymph and the adult engorged female [13].

The parasitic phase (**Figure 1**), begins when the larvae overcome the climatic and host barriers, since its life cycle is influenced by climatic factors acting on the free living tick stage and the host response against the tick as a parasite. Larvae, then reaches the bovine skin, where they will start the physiological processes of feeding, molting and copulation of the larva, nymph and adult stages respectively [14]. The duration of the parasitic phase is relatively constant, it has been estimated that the duration of this stage from larvae to the adult engorged female, occurs approximately from 18 to 22 days, including feeding, molting and change to the next stage; the whole process takes place all the time on the bovine. The mortality

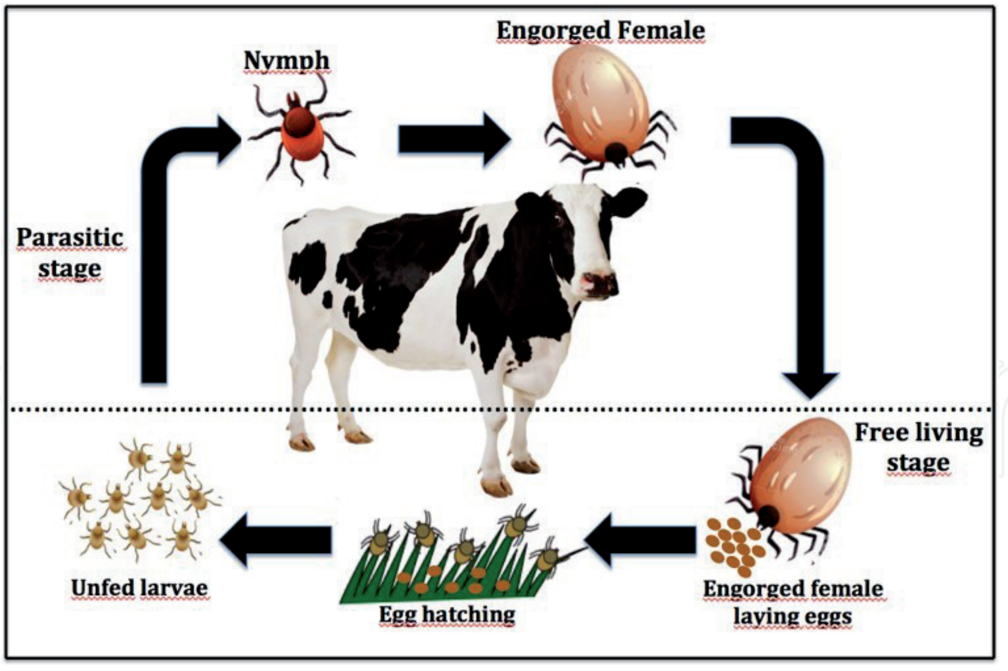

Figure 1.
Life cycle of the one host thelmophagous cattle tick Rhipicephalus (Boophilus) microplus*, showing a parasitic and a free living stage and four different ontological forms: Egg, larvae, nymph and adult or engorged female. (Artwork composed by Fernando Rosario & Delia Inés Dominguez 2021).*

rate of ticks in this phase is determined by the resistance of the host, since, larvae as we already mentioned, is influenced by changing climatic factors as well as the host response against the different tick parasitic stages, the larvae, nymph and the adult engorged female [14].

The non-parasitic phase (**Figure 1**), begins when the engorged female detaches from the host in search of suitable places for oviposition, the eggs laid remain under the grass, until the larvae hatches and appear on the grassland ready to infest the bovine host. Under the grass, the non-parasitic cycle goes through several stages: pre-oviposition, oviposition, incubation and larval hatching. The intervals duration for the completion of each stage, are variable and greatly conditioned by factors such as season, host abundance, selection of host species, and the climatic conditions mainly humidity and temperature [15]. Biologically, these processes involve the physiological and behavioral response of ticks to temperature, moisture stress and day length that result in specific patterns of seasonal population dynamics and hosts availability [14].

R. microplus changes to the juvenile adult stage approximately 13 days after the larva attaches to the bovine host, in this stage male and female become sexually dimorphic. Once the exubia is lost, the male is ready to copulate the next day. The male is very mobile and walks around the host looking for females to mate, regularly male ticks are found below of semi-engorged females. The female is not as mobile as the male and remain attached to the host throughout her life cycle. The female ends her cycle as soon as it finishes laying eggs on the grass (**Figure 1**) [16].

3. Global importance of ticks

Undoubtedly Ticks are the most important group of pathogen vectors causing diseases in wild and domestic animals [5]. Its great economic and sanitary importance is due to its wide distribution, vectorial capacity, hematophagous habits and the number of cattle it affects [17].

The control of tick populations and the diseases they transmit in countries with emerging economies in Latin America, is a prevailing need due to the millionaire economic losses they cause. On the other hand acaricides with a tick-killing effect is the main tool available to control ticks [18].

The cattle fever tick *R. (B.) microplus* and *R. (B.) annulatus* are two of the known vectors of *Babesia bovis* and *Babesia bigemina*, the causative agents of bovine babesiosis [19]. These ticks are invasive livestock parasites (**Figure 2**) in the transboundary region between United States (U.S.) and northern Mexico [19], affecting

Figure 2.
Infested cow from the Northern transboundary region between Mexico and the United States, shows the tick infestations resulting from the intensive use of acaricides based on a regular and systematic chemical application approach. (The photograph has been kindly provided by Dr. Martin Ortiz Estrada).

Figure 3.
Map showing the distribution of the cattle tick Rhipicephalus (Boophilus) microplus *and the current state of tick control officially recognized by the National Tick Campaign Office from the National Center for Verification Services on Animal Health SENASICA from the Mexican Government. Consulted and taken from the official SENASICA web site on August 19, 2021. (https://www.gob.mx/senasica/documentos/situacion-actual-del-control-de-la- garrapata-boophilus-spp).*

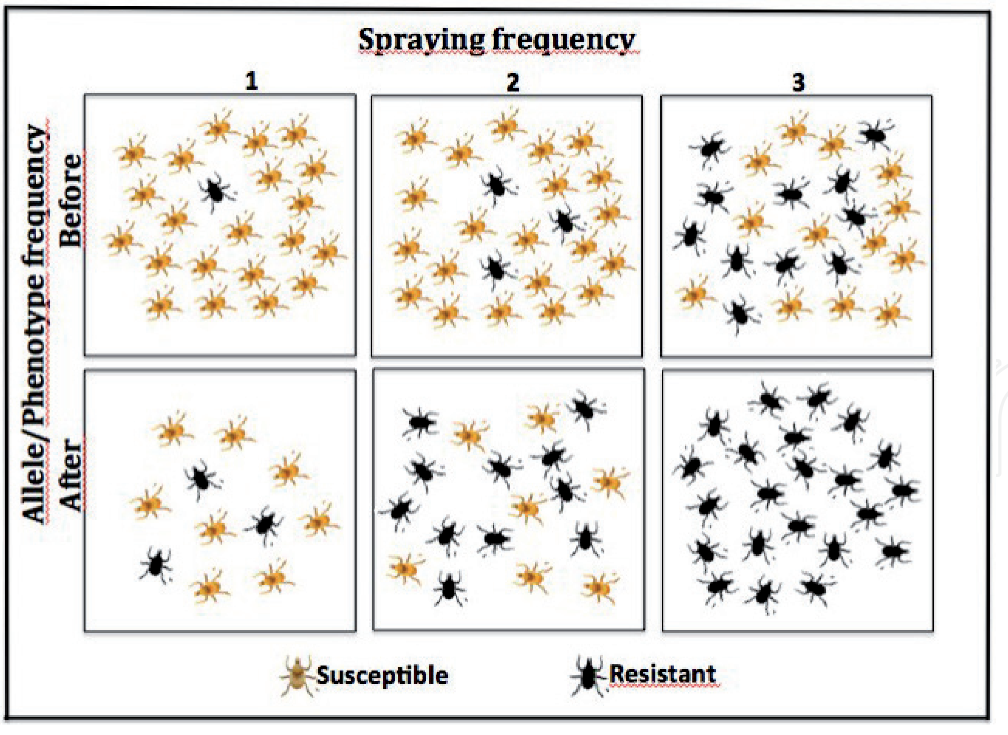

Figure 4.
Theoretical illustration showing the increase of acaricide resistance phenotypes and/or allele frequency levels in a tick population. Some individuals (black) with genetic traits allowing them to survive the acaricide applications can reproduce; if the selection pressure is frequent, they progressively become the preponderant part of the tick population. (Artwork composed by Fernando Rosario & Delia Inés Dominguez 2021).

32 million heads of cattle (**Figure 3**), and are considered to be the most economically important ectoparasites of cattle worldwide [20, 21]. The use of acaricides has an environmental impact as well, originated by the contamination of the soil, and water, besides the killing effect on other beneficial arthropod species and the contamination of food products for human consumption such as milk and meat, derived from this type of livestock operations.

Acaricides have been intensively used for tick control; as a result the use of chemicals combined with the plasticity of tick genomes, has increased progressively the appearance of resistance to different families of acaricides unavoidably (**Figures 2** and **4**) [22], and in many cases to the appearance of multiple resistance. The appearance of resistance in the cattle industry has highlighted the greater inconvenience of the use of acaricides, the selection of resistant tick populations due to the use of acaricides or mixtures of acaricides elaborated based on the ignorance of the resistance mechanisms [22]. There are some critical and basic concepts that allow us to make a road map, on how acaricide resistance occurs, after the continuous and frequent application of chemical treatments. After the continuous exposure, the acaricide kills a fraction of the susceptible ticks, and an increase of tick resistant phenotypes gradually occurs, as illustrated in **Figure 4**. As a consequence, the half-life of pesticides in some regions of northern Mexico has been reduced to such a degree that they no longer represent an alternative to control ticks (**Figure 2**), and the interest of looking for new approaches is currently focused to search for new potentially useful immunogenic vaccine candidates to control resistant tick populations [23].

4. Acaricide resistance in Mexico

Acaricide resistance is a genetic condition driven by randomly arise genetic traits that can be inherited to the progeny and spread throughout the population along time, promoted by natural or artificial selective pressure on a toxic environment, contaminated with synthetic or natural acaricides.

Parasitic diseases have become a global problem due to free trade agreements or commercial exchange of goods and services, because the geographical borders between countries have disappeared from the political geography. One of the biggest issues associated with exportation and importation of animals and products, is the free movement of vector and vector borne diseases associated with animal health and food safety [24], as well as the tick genomes, encoding the acaricide resistance traits that will be transferred to the progeny.

Two general mechanisms of acaricide resistance have been described in *R. microplus*: The enhanced metabolic detoxification, mediated by multigenic families of enzymes (**Figure 5**) such as: esterases, Glutathion-S-Transferases, Mix function Oxidases (Cytochrome P-450) [25, 26], the recently proposed mechanism mediated by the ATP Binding Cassette (ABCt) (**Figure 5**), which is a transporter group of proteins [27], and the target site modification [28–31].

However, the most common mechanism in pyrethroid resistant tick populations in the field, is the target site modification, mediated by a substitution occurring on gene sequences as it was demonstrated for the occurrence of a point mutation located at the segment six domine III (S6III) of the sodium channel gene [30], which encodes the substitution of a Phenylalanine by an Isoleucine in Mexican field samples (**Figure 6**).

Figure 6, show the association between genotypes and phenotypes of nine tick strains that were grouped based on three different phenotypes: very resistant, moderately resistant and susceptible to pyrethroids as measured by the larval packet test (LPT) and later analyzed by the allele specific PCR amplification test in order to identify the three different genotypes (RR, RS and SS) in samples collected from Yucatán, Mexico.

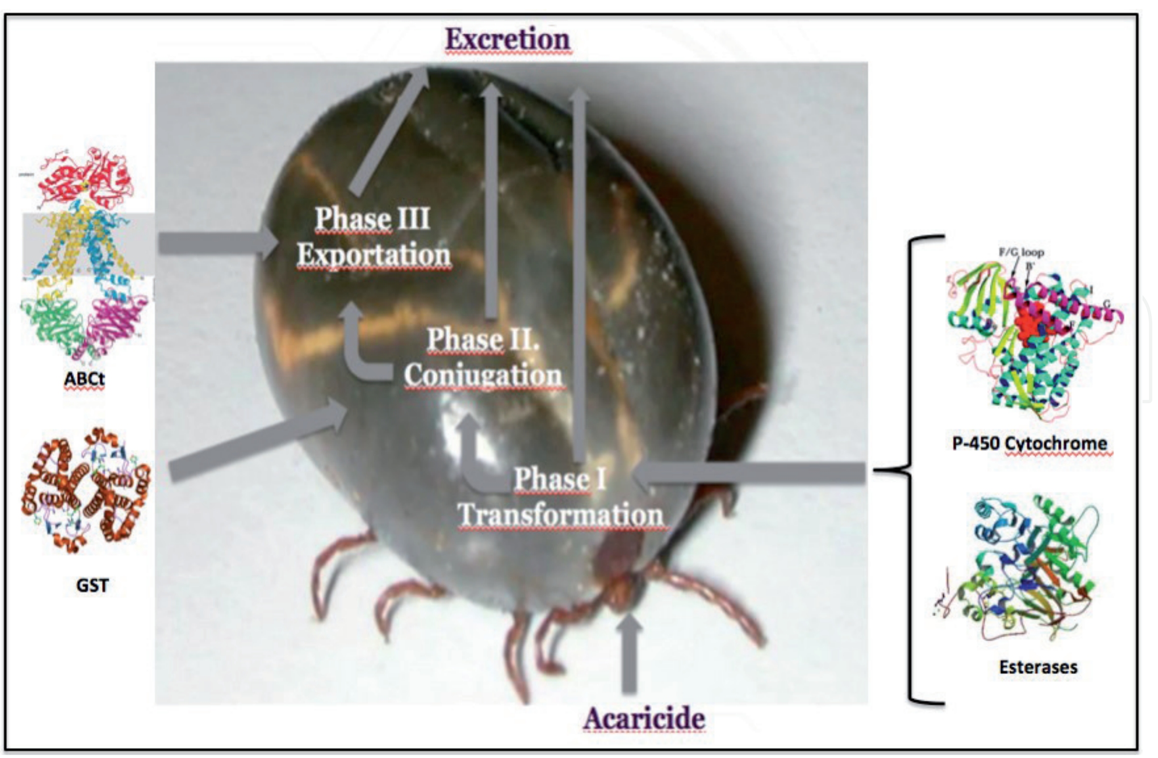

Figure 5.
Illustration showing the different phases of detoxification mechanisms and the participation of multigenic families of hydrolyzing (Esterases and cytochrome P450), modifying enzymes (GST) or the group of transporter proteins ATP binding Cassette (ABCt) at different levels of the metabolic detoxification process (transformation, conjugation and exportation). (Artwork composed by Fernando Rosario & Delia Inés Dominguez 2021).

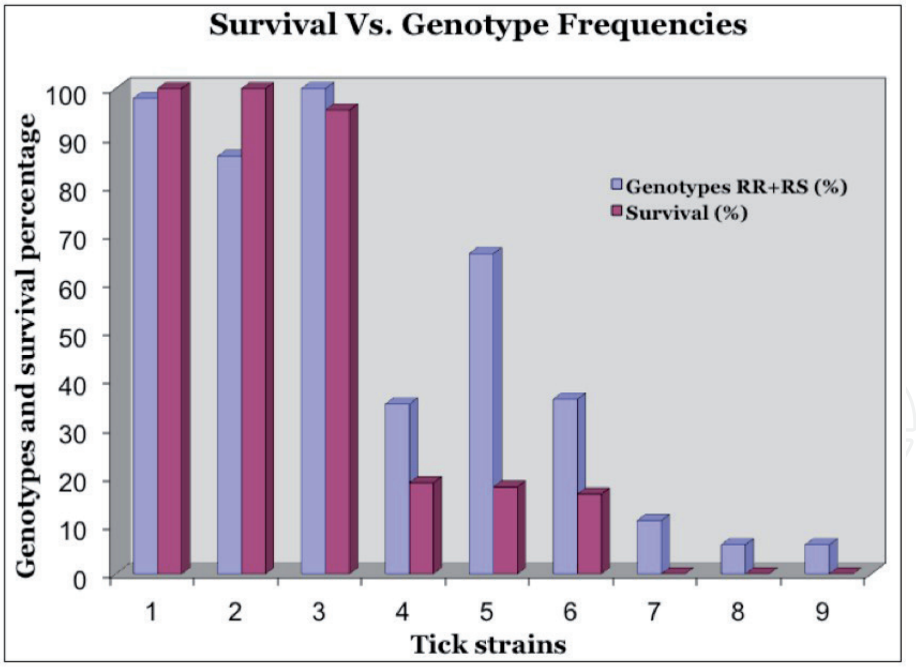

Figure 6.
Genotype and larval survival percentages obtained by the allele specific PCR and LPT respectively, were plotted in order to show the statistical correlation between the presence of the mutation on the sodium channel gene and the resistance to pyrethroids in samples collected from Yucatán, Mexico (p < 0.05). Tick strains were classified by their phenotype as: Very resistant (strains 1, 2 and 3), intermediate resistance (strains 4, 5 and 6) and very susceptible (7, 8 and 9). Genotypes are represented by blue bars and phenotypes by red bars. (Graph from Dr. R. Rosario-Cruz archives).

Results demonstrated that PCR test can be used as a molecular tool to detect and predict the appearance of pyrethroid resistance phenotypes, since a resistant allele frequency lower than ten percent, started showing up in the susceptible strains while they were still susceptible as measured by the LPT [30]. According to this results the genotype and phenotype frequency (**Figure 3**) increases in parallel with the continuous application of acaricides ($p < 0.05$) (**Figure 4**).

Up to date, numerous studies have been reported in order to predict the mode of inheritance of pyrethroid resistance in various insects such as mosquitoes (31), the horn fly *Haematobia irritans* (L), [32], *Plutella xylostella* [33] and *Cydia pomonella* [34]. However, the conclusions obtained from these studies have been made based on measurements of the phenotypic response to toxicological bioassays, and did not take into account the genotypes present in the strains analyzed; therefore, no general conclusions can be made, based on these data, obtained from the phenotypes of these arthropod species.

There are evidences demonstrating that in *R. microplus* the sodium channel substitution, encoding the pyrethroid resistance trait, is inherited to the progeny by a completely recessive mode when the male is resistant and female susceptible (RS), since the heterozygous RS genotype behave as a susceptible phenotype [35], suggesting that resistance to flumethrine (Flu-R) and deltamethrine (Del-R) is due to a single gene recessively inherited, while the Cypermethrin resistant RS genotype (Cyp-R), show a residual 36% of larval survival, suggesting that pyrethroid resistance in Cyp-R SR heterozygous strain, is probably due to different mechanisms. On the other hand pyrethroids as a class show a residual maternal effect for all Flu-R, Del-R and Cyp-R for the SR heterozygous genotype strain obtained from the cross of a susceptible male and a resistant female, since, approximately 30% of the heterozygous progeny behave as a resistant phenotype probably due to a mechanism of resistance different than the sodium channel gene substitution [35] inherited by the resistant female, so called maternal effect.

The use of acaricides has been the most important tool against ticks; however, the abuse of chemical control has led to multiple resistance to different classes of commercially available acaricides [36, 37]. Due to recent problems of multiple resistance, different research groups in Mexico and around the world, have focused on finding different alternatives such as plant extracts with acaricide activity [38] and recombinant proteins, potentially useful for vaccine development as an alternative to control tick infestations caused by *R. microplus* [39] as well as transmission of pathogens.

5. Integrated tick management program

Livestock industry in tropical and subtropical regions of the world, is affected by tick infestations, and the economic losses it causes due to the direct effects associated to their blood-sucking habits, such as skin damage and pathogens transmission in tropical and subtropical areas [5, 12, 40]. The producers also have important losses associated with decreased weight gain and low production of milk and meat due to the economical impact on cattle by pathogens causing Babesiosis (*B. bovis and B. bigmina*) and Anaplasmosis (*A. marginale*) [41, 42]. However, there are no precise information on the contribution of each of these components to the complex network of interactions between the host, the tick and the tick borne pathogens.

The cattle tick control has been traditionally based on application of acaricide strategies, by dip bath, sprying, pour on or injection, ignoring the consequences of frequent acaricide applications and the biology of the vector. In some states of Mexico, multi-resistance is a constant and current threat, which affects the National livestock production and therefore the economy of producers, since they depend completely on the use of acaricides, but do not have access to technical advice from any public or private office, in order to design a control program to prevent the sudden loss of efficacy of the acaricides used for tick control [43].

The most reliable information on global economic losses, date from the 1980s, these figures estimate that one billion head of cattle are exposed to tick infestations in tropical and subtropical regions of the world and in 1984, economic losses were estimated in eight US billion dollars [44].

Reported data in the literature does not include the loss of human life due to ticks and tick borne diseases, such as the thousands of cases of Lyme disease that occur annually in Europe and North America [45, 46], tick-borne encephalitis cases in Europe [47], and tick-borne rocky spotted fever cases in the United States [48].

In the context of animal health, the most important tick is *R. microplus* to which losses in productivity were attributed and quantified in 1987, in more than one US billion dollars annually in South America [49], and in 1974 in Australia, annual losses were estimated at 62 million dollars [50]. Recent studies reported that Brazil losses were quantified in two US billion dollars [51].

Recent experimental trials of an integrated tick management (ITM) program in Mexico, suggest that ITM programs should included the combined use of acaricides with an anti-tick vaccine against *R. microplus* [52]. The application of the ITM program in field facilities, decreased the frequency of acaricide applications by period of time from 27 to 155 days. This extension on the average application time, decreased the number of total annual applications from 14 to 2.8, which mean a reduction in the use and purchase of acaricides of 80%. It is predictable that a proportional reduction of the environmental contamination can be expected by including an anti-tick vaccine within the ITM program. The reduction of costs and use of acaricides was attributed to the effects of the vaccine on the tick reproductive parameters, for instance, the tick weight was reduced in vaccinated cattle, from

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Figure 7.
Comparison of 21 days old adult engorged females, collected from vaccinated and unvaccinated cattle under an integrated tick management program in the coastal state of Guerrero, Mexico. (Photo from Dr. R. Rosario-Cruz archives).

166 mg/tick to 25 mg (**Figure 7**), for example, this tick reduction in size, meant an average egg mass reduction of 84%.

These data was used to calculate the reduction of production costs due to the purchase of pesticides but did not include the purchase of antibiotics to control babesiosis and anaplasmosis, for calculation purposes [52]. The cost of chemical tick control in this study was $ 408.3 Mexican pesos per animal, while the combined program was only $ 128 pesos, which mean a reduction of 68.63% for the purchase of ixodicides.

The extrapolation of these data to the national livestock herd estimated in 30 million head of cattle, is equivalent to 12,248.7 million Mexican pesos. The use of a combined control program would reduce these losses from 12,248.7 million of Mexican pesos to 3,843.7, that is a reduction of 68.63% of the losses applied to the Mexican livestock herd [52].

The data published in this paper shows an estimated annual loss of 942 million USA dollars, (considering a current exchange rate of 20 Mexican pesos/US dollar, the equivalent annual losses would be 612 US million Dollar) it is worth mentioning that this and other previously published papers, does not include the loss of animals dead by ticks and tick borne diseases such as Babesiosis and Anaplasmosis, nor the expenses produced by the costs of the medication used to control these tick borne pathogens which can double the annual losses due to tick infestations.

6. The perspective of immunological approaches

Edward Jenner was the first to scientifically prove in studies carried out in 1796, a method to protect against smallpox, thereby laying the foundations of vaccinology, and although the invention is not directly attributed to him, he is often considered the father of vaccines due to his scientific approach that proved that the "vaccination" method worked, and from then until today, more than 200 years after its discovery, new biotechnological tools have substantially improved not only the application of vaccines, but the way to produce them.

A vaccine is a biological preparation that provides an active acquired immunity to a particular pathogen. The vaccine preparation stimulates the immune system to recognize a foreign threat and thus destroys and remembers it, so that the immune system can easily destroy any of these pathogens when they later invade into the body. The vaccine characteristics can be enhanced by Biotechnology.

Vaccines have been the most significant advance in public health, and its preventive prophylactic treatment has been demonstrated as we mentioned, for over 200 years for bacterial and viral diseases preventing morbidity and mortality in millions of people annually [53]. Vaccine development during the pre-genomic era was based on the use of dead, live or attenuated organism or on the use of subunitarian proteins purified from total extracts from organisms of interest [54].

These subunitarian proteins may contain one or more antigens combined. To develop such vaccines is a critical necessary step, identification of proteins of interest and eliminating others that are not useful. In this particular case, in order to be recognized as protector, an antigen must be able to limit the development or reproduction of the organism, parasite or pest in question in subsequent exposure challenges [55].

The empirical approach to the development of subunit vaccines includes several steps: a) culturing the parasite, microorganism or pest to be controlled, b) the analysis, and identification of its components, c) purification of antigens having immunogenic properties required for product development and d) the subsequent challenge with the infectious agent or parasite against which we want to develop the vaccine, in an appropriate animal model to evaluate the immunogenic characteristics of this technology [56, 57].

This methodology has difficulties inherent in the process of identification and purification of the fractions possessing the optimal antigenic characteristics for vaccine development and the availability of macro or microorganism to be controlled by this biotechnological tool because the vaccine production It is severely limited when the target organism cannot easily grow [58]. There are other drawbacks that have to do also with the biology of the target organism, since in some cases the most abundant proteins are not necessarily immunoprotective, or may be the case that the antigens expressed during in vivo or infestation infection as the case are not the same as those expressed during cultivation in vitro latter may not be the case in ticks [59].

Difficult as it may seems, the hard work has already made great progresses, the number of cloned and analyzed genes are already a big list, and experiments have shown that genes as Bm86, subolesin, ferritin, aquaporin and a growing number of orthologous genes can be used to control ticks. The future in the field of vaccine development is becoming shorter, and the scope of modern technology in the field is increasingly longer. Landing knowledge regarding the tick vaccines development for tick control, is very close to pays off as seen by the growing list of new antigens discovered, although the tick control still represents a challenge for the scientific community.

7. Conclusive remarks

Ticks and tick-borne pathogens constitute a growing problem for human and animal health worldwide, since, they are considered, the most important vectors of disease-causing pathogens in wild and domestic animals and the second most important vector of pathogens causing diseases in humans, only after the mosquitoes.

Resistance to acaricides impacts directly the economy and the competitiveness of producers, and its presence within the ranches implies the expenses associated to control of ticks and tick borne diseases. Efficient integrated control programs are required to mitigate the direct effects on cattle infested with resistant ticks, and to keep a low prevalence of tick borne diseases.

The use of an integrated tick management program in Mexico, including a combined control strategy (acaricides and tick vaccine), reduced the use of acaricides for tick control by 80% approximately, with a cost–benefit ratio of 3:1, lowering the environmental and food products contamination derived from this activity, reducing the mortality attributed to Babesiosis and Anaplasmosis and contributing to the development of a sustainable, and environmentally friendly livestock production system.

New candidate protective antigens and research on tick vaccine development need to be addressed to establish and design better strategic control programs, since vaccines have demonstrated to be the most effective and an environmentally friendly intervention for the control of tick infestations and tick-borne diseases.

The hard work, difficult as it may seems, has already made great progresses, the future in the field of tick vaccine development is becoming shorter, and very close to pays off as seen by the growing list of new antigens discovered, although the tick control still represents an innovation challenge for the scientific community in Mexico and all over the world.

Conflict of interest

The authors declare having no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript.

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