The control of Hyalomma ticks, vectors of the Crimean–Congo hemorrhagic fever virus: Where are we now and where are we going?

Sarah Bonnet, Gwenaël Vourc'h, Alice Raffetin, Alessandra Falchi, Julie Figoni, Johanna Fite, Thierry Hoch, Sara Moutailler, Elsa Quillery

REVIEW

The control of *Hyalomma* ticks, vectors of the Crimean–Congo hemorrhagic fever virus: Where are we now and where are we going?

Sarah I. Bonnet[1,2]*, Gwenaël Vourc'h[3,4], Alice Raffetin[5,6,7], Alessandra Falchi[8], Julie Figoni[9], Johanna Fite[10], Thierry Hoch[11], Sara Moutailler[12], Elsa Quillery[10]

1 Animal Health Department, INRAE, Nouzilly, France, **2** Ecology and Emergence of Arthropod-borne Pathogens Unit, Institut Pasteur, CNRS UMR 2000, Université Paris-cité, Paris, France, **3** Université Clermont Auvergne, INRAE, VetAgro Sup, UMR EPIA, Saint-Genès-Champanelle, France, **4** Université de Lyon, INRAE, VetAgro Sup, UMR EPIA, Marcy l'Etoile, France, **5** Reference Centre for Tick-Borne Diseases, Paris and Northern Region, Department of Infectious Diseases, General Hospital of Villeneuve-Saint-Georges, 40 allée de la Source, Villeneuve-Saint-Georges, France, **6** EA 7380 Dynamyc, UPEC, Créteil, France, **7** Unité de recherche EpiMAI, USC ANSES, Ecole Nationale Vétérinaire d'Alfort, Maisons-Alfort, France, **8** UR7310, Faculté de Sciences, Campus Grimaldi, Université de Corse, Corte, France, **9** Santé publique France, 94410 Saint-Maurice, France, **10** French Agency for Food, Environmental and Occupational Health & Safety, 14 rue Pierre et Marie Curie, Maisons-Alfort Cedex, France, **11** Oniris, INRAE, BIOEPAR, Nantes, France, **12** ANSES, INRAE, Ecole Nationale Vétérinaire d'Alfort, UMR BIPAR, Laboratoire de Santé Animale, Maisons-Alfort, France

* sarah.bonnet@inrae.fr

Abstract

At a time of major global, societal, and environmental changes, the shifting distribution of pathogen vectors represents a real danger in certain regions of the world as generating opportunities for emergency. For example, the recent arrival of the *Hyalomma marginatum* ticks in southern France and the concurrent appearance of cases of Crimean–Congo hemorrhagic fever (CCHF)—a disease vectored by this tick species—in neighboring Spain raises many concerns about the associated risks for the European continent. This context has created an urgent need for effective methods for control, surveillance, and risk assessment for ticks and tick-borne diseases with a particular concern regarding *Hyalomma* sp. Here, we then review the current body of knowledge on different methods of tick control—including chemical, biological, genetical, immunological, and ecological methods—and the latest developments in the field, with a focus on those that have been tested against ticks from the genus *Hyalomma*. In the absence of a fully and unique efficient approach, we demonstrated that integrated pest management combining several approaches adapted to the local context and species is currently the best strategy for tick control together with a rational use of acaricide. Continued efforts are needed to develop and implement new and innovative methods of tick control.

Author summary

Disease-bearing *Hyalomma* ticks are an increasingly emerging threat to humans and livestock worldwide. Various chemical, biological, genetic, and ecological methods for tick

Check for updates

OPEN ACCESS

Citation: Bonnet SI, Vourc'h G, Raffetin A, Falchi A, Figoni J, Fite J, et al. (2022) The control of *Hyalomma* ticks, vectors of the Crimean–Congo hemorrhagic fever virus: Where are we now and where are we going? PLoS Negl Trop Dis 16(11): e0010846. https://doi.org/10.1371/journal.pntd.0010846

Editor: Ran Wang, Beijing Children's Hospital Capital Medical University, CHINA

Published: November 17, 2022

Funding: The author(s) received no specific funding for this work.

Competing interests: The authors have declared that no competing interests exist.

control have been developed, with variable efficiencies. Today, the best tick control strategy involves an integrated pest management approach.

Introduction

Ticks have a worldwide distribution, occupy a wide variety of biotopes and comprise about 900 species, some of them being able to transmit viruses, bacteria, and/or parasites [1]. In the Northern Hemisphere, they are the primary vectors of both human and animal pathogens, and in the Southern Hemisphere, they are the primary vectors of importance in animal health [2]. Socioeconomic and climate trends drive changes in the geographic distribution and seasonality of several tick species, their vertebrate hosts, and the reservoirs of pathogens, shaping the persistence of pathogen foci since the beginning of the 20th century [3–8]. Thus, the question of the consequences of the introduction and/or permanent establishment of new tick species with their pathogens in areas previously devoid of them is now center stage. Ticks of the genus *Hyalomma* represent a perfect example associated with this risk of emergence [9]. In fact, *Hyalomma marginatum* is regularly introduced—but to date unable to establish itself—via migratory birds in Northern Europe [10–12]. However, the recent establishment of this species in the South of France [13], along with the occurrence of Crimean–Congo hemorrhagic fever (CCHF) cases in recent years in Spain [14], raises many concerns about the associated risks for the European continent.

Currently, 27 species are recognized within the genus *Hyalomma* and are present on all continents except in North and South America [15]. Their distribution is conditioned by their preference for open spaces with relatively hot and dry climates (semidesert steppes, savannas, Mediterranean scrubland, etc.) (Fig 1). Like all hard ticks, *Hyalomma* have 3 developmental stages: larvae, nymphs, and adults (males and females), each of which takes only 1 blood meal. The majority of *Hyalomma* species have a triphasic cycle, with larvae and nymphs mostly choosing small vertebrates in sheltered habitats as hosts, whereas adults mainly feed on large ungulates including livestock (Fig 2). The *Hyalomma* species most frequently infesting humans are *Hy*. *anatolicum*, *Hy*. *marginatum*, and *Hy*. *aegyptium* [16,17]. *Hyalomma* spp. adults have generally an ambush behavior towards their host. They have low self-dispersal, but can nonetheless be transported over long distances by their hosts during their blood meal [18].

A large number of pathogens—parasitic, viral, or bacterial—have been mentioned in the scientific literature as being transmitted or potentially transmitted by ticks from the genus *Hyalomma*; all have animal reservoirs and some cause zoonoses [19]. Nevertheless, very few vector-competence experiments have been conducted due to the difficulties in carrying out a complete cycle under experimental conditions (the need for "healthy" tick colonies, for vertebrate hosts adapted to both ticks and pathogens or for an efficient artificial tick feeding technique, for pathogen cultures, as well as for high biosafety level facilities, etc.). Among the viruses for which transmission by some *Hyalomma* species has been proven are the CCHF virus [20], the Dugbe virus [21], the West Nile virus [22], the Venezuelan equine encephalitis virus [23], the African horse sickness virus [24], and the Kyasanur Forest disease virus [25]. Among bacteria, some *Hyalomma* species are involved in the transmission of *Rickettsia aeschlimannii* [26], *Anaplasma marginale* [27], and *Coxiella burnetii* [28,29]. Finally, *Hyalomma* species can transmit to cattle *Theileria annulata*, the agent of tropical theileriosis (TT), or Mediterranean theileriosis, *Theileria orientalis*, the agent of oriental theileriosis [30], and *Babesia occultans* [26,31]. In small ruminants, they transmit *Theileria lestoquardi* and *Theileria ovis* [32,33], and in equids *Theileria equi* and *Babesia caballi* [34,35]. Apart from pathogen

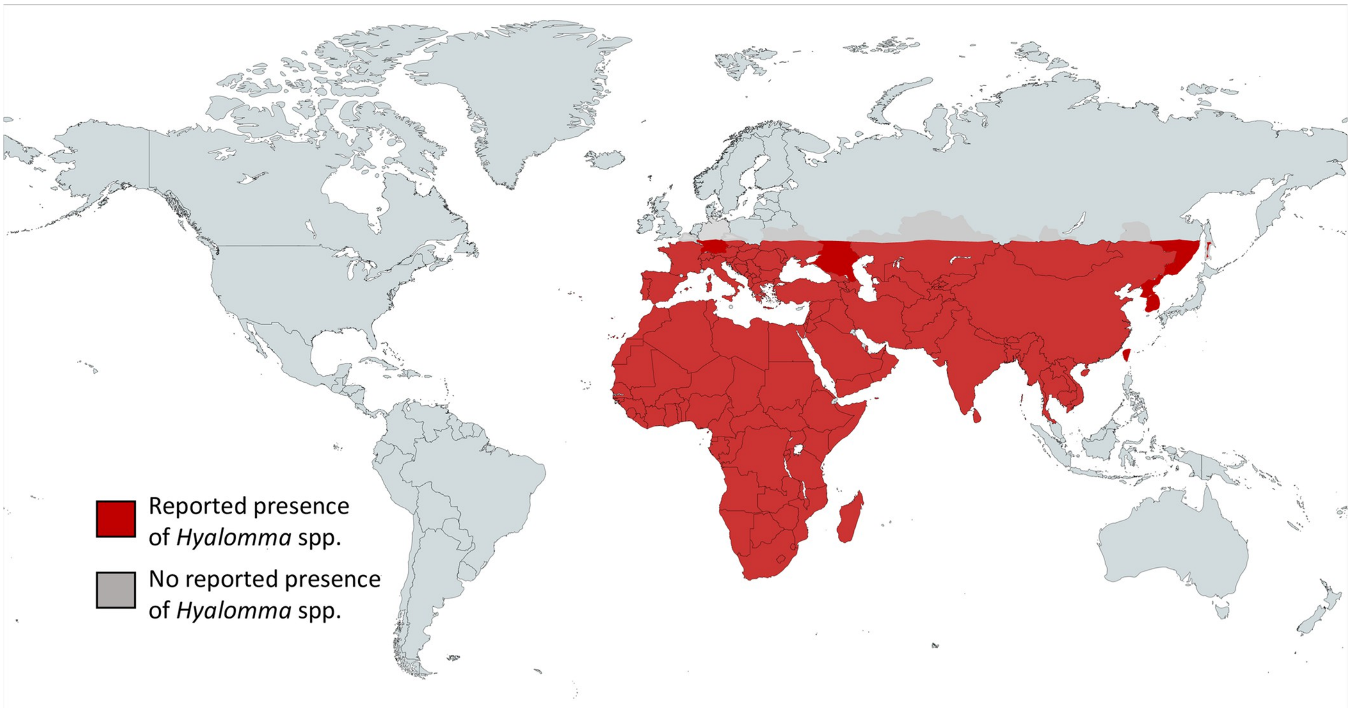

Fig 1. Global geographic distribution of *Hyalomma* spp. ticks. Created with mapchart.net.

https://doi.org/10.1371/journal.pntd.0010846.g001

transmission and in addition to significant blood spoliation, *Hyalomma* ticks also generate serious wounds that can become superinfected during the bite due to their long mouthparts [36,37].

The evidence for the medical and veterinary importance of *Hyalomma* species continues to accumulate over time. As with all other arthropod vectors, effective control of these ticks can only be achieved with a good understanding of the biology and ecology of the species in their natural habitat. In the context of increasing resistance to acaricides, integrated control of these arthropods is to be favored. Integrated control is based on the rational application of a combination of chemical, physical, biological, genetic, ecological, or animal population selection measures to keep the presence of vectors below a certain threshold of pathogen transmission or economic loss. Here, we explore the current body of knowledge on the various tick control methods and the latest developments in the field, with a special focus on the results obtained for *Hyalomma* ticks.

Chemical control

The use of acaricides in tick control dates back to the late 19th century, with the use of baths containing arsenic derivatives to eliminate *Rhipicephalus microplus* [38], and remains the main method of tick control used today. Acaricides are still applied directly to the vulnerable host subject to tick infestation, either by spraying or bathing individuals with aqueous acaricide formulations, or by topical treatments on the back (with a "pour-on" formulation). Exceptionally, in the case of massive infestation by endophilic ticks on a farm, the application of acaricides to the walls of stables may be recommended [39]. However, in the case of *Hy*. *scupense*, for example, this technique is only marginally effective because nymphs can penetrate even deep cracks and crevices [39]. Due to the appearance of tick populations resistant to certain insecticides and their strong negative impact on the environment, arsenic derivatives,

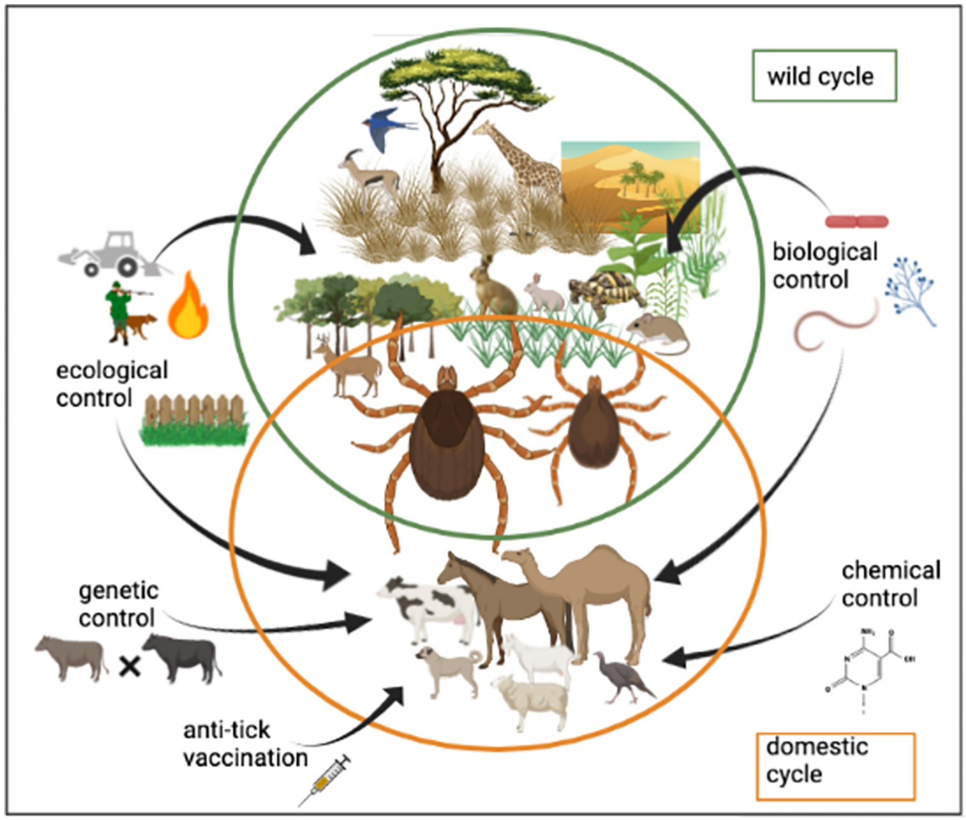

Fig 2. Schematic representation of the different control methods applicable to *Hyalomma* ticks for consideration in the context of integrated pest management. Created with BioRender.com.

https://doi.org/10.1371/journal.pntd.0010846.g002

organochlorines, and then organophosphates were abandoned in the 1970s in favor of pyrethroids (e.g., deltamethrin, permethrin, flumethrin), which inactivate sodium channels [40], neurotoxins such as fipronil and amitraz [41], growth inhibitors such as fluazuron [42], or activators of invertebrate glutamate-dependent chloride channels such as macrocyclic lactones (e.g., eprinomectin, ivermectin, moxidectin) [43].

To date, resistance to all of these substances has been identified in ticks, making their effectiveness increasingly uncertain [44]. Although most of the studies carried out on tick population control using chemical acaricides, or resistance to them, involve species of *Rhipicephalus* (*Boophilus*)—monotropic ticks that infest cattle in many regions of the world and thus subject to very strong selection pressure [44]—, a few studies have focused on *Hyalomma* sp. suggesting that resistance in certain populations is emerging, especially in Asia. In Pakistan, tests conducted in 2009 did not show resistance to ivermectin or cypermethrin in *H. anatolicum* [45], but resistance to fipronil and ivermectin was identified in 2021 [46]. These 2 studies had unsurprisingly identified both a misuse of acaricides over exceedingly long periods of time (often coupled with low concentrations or inadequate doses) and lack of product rotation as risk factors for the development of resistance. In India, other populations of *H. anatolicum* have been identified as resistant to deltamethrin and diazinon as well as fipronil and cypermethrin [47–49]. Resistance to emamectin benzoate, spirotetramat, and hexaflumuron has also been reported in populations of *H. asiaticum* in China [50]. In contrast, a 1996 study showed the efficacy of flumethrin as a pour-on for camels against *H. dromedarii* [51]. The efficacy of an amitraz/cypermethrin pour-on mixture was also validated for *H. rufipes* infesting buffaloes in South Africa in 2005 [52].

In addition to the development of acaricide resistance, the negative impacts of acaricides include contamination of livestock production (milk and meat) and the environment, including non-target animals [53]. For this reason, research is being carried out to identify new acaricide substances that are more "natural" and/or less damaging to the environment, such as substances derived from plants, essential oils, or nanoparticles. Validating their efficacy and formulations adapted for administration to animals is, however, time consuming and still requires research [54–56]. A recent comprehensive list of plant-derived substances tested against *Hyalomma* species is presented in a recent review [57]. A 2017 review also presents the efficacy levels of metal and metal oxide nanoparticles tested as acaricides against ticks with a high level of toxicity to *H. anatolicum* and *H. isaaci* larvae [58]. The value of using tick hormones has also been evaluated in other species and has been shown to increase the efficacy of acaricides after inclusion in "a permethrin-impregnated oily matrix" [59], or coupled with a "tail-tag decoys" in cattle [60,61]. In addition, traps using these pheromones coupled with or without CO_2 have also been developed with some success against *Amblyomma* spp. [62,63]. However, the trials carried out have not led to the marketing of these traps.

Biological control

Ticks have a number of natural enemies (bacteria, fungi, spiders, ants, beetles, hymenopterans, rodents, birds, etc.), and several studies have investigated control methods that can take advantage of their action.

Among the entomopathogenic fungi evaluated for activity against ticks, *Beauveria bassiana*, *Lecanicillium (Verticiliium) lecanii*, and *Metarhizium anisopliae* have been the most studied [64]. They have been commercially developed as biopesticides. Results show that the pathogenicity of the fungus depends on the tick species, tick life stage, tick feeding intensity, the fungus strain, and also the weather conditions and the season in which the conidia are deployed [64]. For example, very encouraging results have been obtained, both in vitro and in vivo by ground spraying with solutions containing *M. anisopliae* conidia, either against *R. microplus (*reviewed in [65]), or against *Ixodes scapularis* [66]. A few trials have been also conducted with entomopathogenic nematodes [67], or with bacteria such as *Bacillus thuringiensis* [68].

Experiments have also been carried out with a tick parasitoid hymenopteran, *Ixodiphagus hookeri*. In the first half of the 20th century, attempts to control ticks by releasing *I. hookeri* were carried out in the United States against *Dermacentor* ticks and in the Soviet Union against *Ixodes ricinus* ticks [69]. Though initially effective, these releases did not prevent the tick population from maintaining itself, probably due to the much higher fertility of ticks compared to the parasitoid wasps [69]. More recently, a trial was conducted in Kenya where 150,000 parasitoids were released in 1 year on a 4-ha pasture occupied by 10 tick-infested cattle [70]. The results showed an impact on *Amblyomma variegatum* ticks, with 50% of the ticks being parasitized by *I. hookeri*, and a reduction in the tick infestation of cattle, but a parallel increase in the *Rhipicephalus appendiculatus* tick population. Above all, it appeared that it was necessary to release parasitoid wasps frequently to obtain significant effectiveness. Moreover, for *I. ricinus* ticks and under natural conditions, there is a balance between the ticks and the parasitoids, the latter infecting only a small proportion of the ticks and having no effect on the global population [71].

Among vertebrate predators, few are specialized in eliminating ticks, with the exception of oxpecker birds (*Buphagus erythrorhynchus* and *B. africanus)*. A study performed in South Africa on birds in captivity showed that they can eat up to 100 engorged females of *Rhipicephalus decoloratus* or more than 7,000 larvae of *Amblyomma hebraeum* per day [72]. However, the use of these birds for effective biological control is unlikely to be feasible. In Africa, it has also been observed that chickens can be effective in controlling ticks, which they consume in large numbers [73,74].

Other invertebrate predators with a significant impact on ticks are species of *Lycosa* (wolf spiders) and especially ants. For example, in some areas of Australia favorable to *R. microplus* ticks, the absence of ticks has been attributed to the predatory action of ants [75]. Petney and colleagues [76] suggest that ant predation on free ticks is higher than generally reported and may even be a factor determining population size. Ants of the genus *Solenopsis* have also been observed feeding on engorged females of *Rhipicephalus* (*Boophilus*) or *Amblyomma* [76–79]. However, the predatory activity of ants is extremely variable and unpredictable in the field and precise data are scarce [75,80].

With specific regard to *Hyalomma*, trials have been carried out with fungi, nematodes, and entomopathogenic bacteria. A commercial formulation of the *Beauvaria bassiana* fungal species was sprayed in rabbit holes to control *H. lusitanicum* in Spain. The quantity of ticks collected from rabbits 30 days after treatment was reduced by almost 80% in spring, but by only 36% in summer, pointing to the importance of temperature on the effectiveness of biocontrol based on fungi [81]. When tested in vitro on engorged *H. anatolicum* females, this fungus also showed a synergistic effect when used with deltamethrin [82]. When used alone, *B. bassiana*, like *M. anisopliae*, induces 90% mortality in these same ticks [82]. The in vitro efficacy of *M. anisopliae* against all stages of *H. anatolicum* collected in Sudan was then confirmed [83], as well as that of *Scopulariopsis brevicaulis* against adult tick stages [84]. Finally, a study demonstrated, in vitro, an effective ovicidal effect of proteases produced by *Aspergillus sojae* and *A. oryzae* on *H. dromedarii* eggs [85]. Biological control trials on *Hyalomma* ticks using entomopathogenic nematodes have also been carried out in laboratory conditions, and high virulence of different strains of *Steinernema* sp. and *Heterorhabditis* sp. has been reported against *H. dromedarii* and *H. excavatum* [86–88]. Finally, *B. thuringiensis* can act on the hemocytes of *H. dromedarii*, suggesting a possible toxic action of this bacterium against this tick species [89].

Although currently, in addition to their high costs, none of these methods taken alone have proven to have sufficient effectiveness on a large scale, some have shown encouraging results, making it possible to consider their use in the context of integrated pest management [90]. Nevertheless, in addition to questions of stability of the results obtained over time and the method of application, before implementing them on a large scale in the field, it will be necessary to ensure that non-target arthropod fauna is not affected.

Genetic control

Genetic control of arthropod vectors consists in altering/modifying their reproductive potential or other functions of interest to combat the vectors or the pathogens they transmit via modifications to their genetic make-up. The genetically modified vectors are then released into the wild to compete with natural populations. The success of such a control strategy therefore depends, among other things, on the existence of a selective advantage of the replacement population. Here, under the term "genetic control," we also include the selection of animal breeds that are naturally more resistant to tick infestation.

Despite recent progress in tick genetic manipulation [91], the possibilities for implementing genetic tick control strategies are very limited. Firstly, breeding large numbers of ticks in the laboratory, an integral part of this strategy, is not an easy task [92]. In addition, the low dispersal capacity of ticks in the natural environment—even though they can travel long distances via their hosts during their blood meal—and their biology, including very long development cycles, represent an obstacle to the replacement of natural populations by genetically modified ones [18]. Finally, in addition to the lack of data on tick genomes, which hinders the identification of potential targets for genetic control, the release of genetically modified organisms into the wild currently raises numerous questions (ethical, legal, logistical, etc.). However, as early as 1976, laboratory irradiation trials had shown the effectiveness of sterilizing *H. anatolicum* males [93]. Irradiation doses sufficient for the production of sterile males that still compete with untreated males for mating with females, thus limiting female fertility, were then established for *H. anatolicum* [94,95], *H. marginatum* [96], and *H. excavatum* [97]. Sterilization of males is also possible in *Dermacentor variabilis* by blocking *subolesin* expression through RNA interference [98]. Nevertheless, to our knowledge, no field release trials of sterile males have been carried out to date for ticks.

The existence of tick-resistant cattle breeds was observed as early as 1912 in Australia in a Jersey herd infested with *R. microplus*: Some animals were always less infested than others, and the trait appeared to be hereditary (see review by Burrow and colleagues [99]. Since then, a number of studies have demonstrated the existence of breeds that are more or less resistant to ticks, with variable heritability of the trait. For example, *Bos indicus* (zebu) is more resistant to infestation by *R. microplus* or *Amblyomma americanum* than *Bos taurus* (cattle) [100,101]. One study identified 3 key pathways in this phenomenon, represented by genes differentially expressed in resistant individuals: the development of the cell-mediated immune response, structural integrity of the dermis, and intracellular Ca^{2+} levels [102]. Another study suggests the involvement of the interferon-gamma pathway [103]. In the 1970s, several cattle breeds resistant to *R. microplus* were thus created, selected, and bred in Australia: Australian Friesian Sahiwal [104], Australian Milking Zebu [105], and Australian Illawarra Shorthorn [106]. However, they were met with mixed success, with farmers preferring the use of acaricides against which ticks had not, at the time, developed much resistance [107]. Work on the Belmont Adaptaur cattle breed shows that tick resistance can be increased to very high levels via selection [108]. More recently, a cross-breeding trial between sires and dams with low *A. variegatum* infestation was conducted in Goudali zebu cattle in Cameroon, but without conclusive results [109]. Resistance is reflected in the rejection of ticks (especially larvae), a lower gorging rate and thus lower weight in females despite an increased attachment time, and a lower hatching rate. In the 1990s, breeding resistant cattle was presented as a promising approach to control tick populations [110], but this has not yet led to applications usable by farmers and no significant progress has been made on the subject since 2000 [111].

The majority of studies have since focused on *R. microplus*, a single-host tick species [112]. However, both innate and acquired resistance to ticks has also been observed with 2- or 3-host ticks, such as *Amblyomma* spp. [100,113–115] or *Ixodes* spp. [116], but also *Hyalomma* spp. Studies have shown acquired resistance to *H. anatolicum* bites in rabbits [117–119] and in crossbred (*B. indicus* X *B. taurus*) calves [120,121]. In South Africa, reports indicate that indigenous Nguni cattle are less infested with *Hyalomma* sp. than Bonsmara or Hereford cattle [115] and that Brahman cattle are less infested with *H. rufipes* than Simmental cattle [122]. Studies in the Gambia have also shown better resistance to *Hyalomma* sp. infestation in N'dama (*B. taurus*) cattle than in the Gobra (*B. indicus*) breed [123]. In Ethiopia, the local Arssi breed was found to be the most resistant to *H. rufipes* bites, followed by the Boran breed, and Boran x Friesian crossbred cattle were the least resistant [124]. Finally, a study in Morocco also showed that a local breed was more resistant to *H. marginatum*, *H. detritum*, *H. anatolicum*, and *H. lusitanicum* than Friesian cattle [125].

Anti-tick vaccination

The evidence of natural immunity to tick bites, identified as early as the beginning of the 20th century (see recent reviews: [111,126]), and capable of providing indirect protection against tick-associated diseases, has naturally led the scientific community to consider anti-tick vaccine control strategies. By targeting the vector, anti-tick vaccines have the dual advantage of combating both the ticks themselves and the direct losses they cause, as well as all potentially transmitted pathogens [127]. Two main types of anti-tick vaccines have been developed, those using antigens exposed to host immune responses during gorging, such as salivary antigens, and those that rely on canceled molecules not exposed to the host immune system [128]. When a tick feeds on a vaccinated animal, it will ingest the antibodies induced by the vaccination, which will diffuse throughout the tick body and inhibit the targeted functions: digestive functions in the digestive tract, anticoagulant, immunosuppressive or anti-inflammatory functions in the salivary glands, or those involved in the multiplication and/or transmission of pathogens. As a result, the tick may be prevented from feeding or digesting, may be rejected by the host immune system, and/or there will be no transmission of microorganisms to the host [129–133]. However, the development of this anti-tick vaccination strategy faces many challenges including the lack of genomic data on ticks, the difficulty of obtaining experimental models, the cost of development and competition with the acaricide industry, as well as the selection of the vertebrate hosts that need to be vaccinated, particularly for multi-host species [134].

Thus, despite extensive research on the subject, only 1 vaccine against *R*. *microplus* is currently marketed in Cuba as Gavac and used in many Central and South American countries [135,136]. In controlled field trials in Cuba, Brazil, Argentina, and Mexico, the Gavac vaccine shows 55% to 100% efficacy in controlling *R*. *microplus* infestations in grazing cattle 12 to 36 weeks after the first vaccination [137]. A similar vaccine was previously marketed in Australia, where it was originally developed, under the name TickGARD [136]. These vaccines are based on a tick digestive tract antigen (Bm86) and generate an immune response that interferes with the digestion of the blood meal and thus decreasing the tick population, the number of eggs laid by females being directly related to the volume of ingested blood [138]. Although this vaccine provides proof of feasibility for anti-tick vaccination, it has the disadvantage of being effective almost exclusively against *R*. *microplus*, with notable variations in efficacy depending on tick populations and regions of the world, and of being expensive, particularly due to the booster shots required [139].

Could this vaccine be used against *Hyalomma*? Several studies have been conducted, with contrasting results. Vaccination with Bm86 showed no effect on infestations of cattle with adult *H*. *scupense* or *H*. *excavatum* ticks [139]. In contrast, an earlier study showed that vaccination of cattle with Bm86 resulted in a 30% reduction in the number of engorged *H*. *anatolicum* nymphs, and even a 95% reduction in the number of feeding nymphs for *H*. *dromedarii* [140]. A similar result was subsequently reported with 89% reduction in the number of feeding nymphs for *H*. *dromedarii* in vaccinated cattle, but the vaccine was less effective in camels, with a reduction in feeding nymph numbers of only 27% [141]. Furthermore, this type of vaccine will be more effective for monotropic species such as *R*. *microplus* that feed almost exclusively on 1 animal species and have a rapid cycle with several generations per year [129]. For broad host-spectrum species with a single annual generation, vaccination must eliminate the tick as soon as it attaches or prevent the transmission of pathogens in the vaccinated animals [132]. Vaccination can even target wild animals: A recent vaccination trial in deer reduced infestation with different tick species, including *H*. *marginatum* and *H*. *lusitanicum* [142].

However, research has turned to the identification and use of Bm86 orthologs in other tick species, including some belonging to the *Hyalomma* genus, because the ineffectiveness of the Bm86-based vaccine against various *Hyalomma* species (including *H*. *excavatum* and *H*. *marginatum*) has been attributed to the large sequence variations identified in the homologous proteins of these species [143]. Vaccination against Haa86, a homolog of Bm86 in *H*.

anatolicum, has shown a protection rate of 60% to 82% depending on the study and has been shown to reduce transmission of *T. annulata* in cattle [144–146]. Vaccination of cattle against Hd86, a Bm86 homolog in *H. scupense*, showed a 59% reduction in the number of engorged nymphs, but no impact on adults [147–149]. More recently, ATAQ, a protein paralogous to Bm86, has been identified in the gut and Malpighian tubules of all Metastriata group of hard ticks (i.e., *Rhipicephalus*, *Amblyomma*, *Hyalomma*, *Dermacentor*, *Haemaphysalys*, and *Bothriocroton* genera) [150]. Although no vaccination trials have yet been carried out, ATAQ appears to be a promising vaccine candidate due to its homology with Bm86 and its conservation across several genera.

The majority of studies investigating the possibility of using other molecules than Bm86 or its orthologs as vaccine candidates to protect against *Hyalomma* sp. infestation have focused on *H. anatolicum*. Immunization with extracts of this tick has shown a decrease in tick feeding in several studies, in some cases with a decrease in transmission of *T. annulata* [151–158]. A subolesin homolog that has shown some efficacy against *R. microplus* has been identified in *H. anatolicum*, but there have been no vaccine trials to date [159]. In another study, subolesin, calreticulin (CRT), and cathepsin type L (CathL) show some reduction of feeding capacity of *H. anatolicum*, on the order of 65%, 41%, and 30%, respectively [160]. In cattle, immunization with ferritin-2 (FER2) and tropomyosin (TPM) has recently shown protection rates against *H. anatolicum* larvae and adults between 51% and 66% [161]. Finally, vaccination trials of rabbits with glycoproteins extracted from *H. dromedarii* showed a slight decrease in the reproductive index of engorged females and a significant reduction in egg-hatching rates [162].

With the exception of Bm86 (for certain tick populations), no tick antigen has thus far been shown to be sufficiently effective in protecting against tick infestation or pathogen transmission. It is likely that the implementation of effective vaccination would require the use of several antigens responsible for partial blockage of feeding and/or pathogen transmission in a "cocktail" vaccine [163]. Thus, very recently, in silico studies have led to the construction of an as-yet untested vaccine candidate that would include both structural protein epitopes of the CCHF virus and subolesin as an antigen against ticks in order to offer dual protection against CCHF transmission [164].

Ecological control

Ecological control, which consists of creating unfavorable conditions in the environment for the ticks to complete their cycle, mainly targets the environment and the tick–host populations [69,165,166]. Another mode of action is to act directly on the probability of encounter between ticks and their hosts [167]. Most of the available literature on these methods involve family *Ixodidae* ticks, but the same principles can be considered for *Hyalomma*.

Environmental modification can have a direct role in affecting tick activity and survival. For example, clearing low vegetation has been shown to be effective in reducing populations of *I. ricinus* [168] or *A. americanum* [169]. Fire can also have a direct effect on tick survival as well as an indirect effect via the impact on host populations and vegetation, and annual burns constitute an effective method of tick control [170]. For example, temporary reductions in tick populations have been observed for *I. scapularis* after fires [171]. But the challenges and risks associated with this practice mean that the use of fire to control tick populations should be considered with great caution, especially because fires have also been associated with increases in *A. americanum* (presumably because deer were attracted to the renewed vegetation growth) [172] or *R. appendiculatus* [173], or with no effect on *Ixodes pacificus* in California [173]. It has also been suggested that the use of plants that are repellent or toxic to ticks could limit their populations [69]. Experimentally, Civitello and colleagues [174] showed that Japanese stiltgrass

(*Microstegium vimineum*) increases the mortality of *A*. *americanum* and *D*. *variabilis*. However, this strategy seems difficult to implement over large areas and would require these species to be highly dominant [175]. In addition, environmental modification can have an indirect role on tick populations by affecting host abundance and diversity, and thus the probability of contact between a tick and a host.

Most ticks have trophic preferences, attaching and feeding more easily and efficiently on certain animal species. Thus, the control of these host species, mainly through hunting or exclusion with barriers, can have an impact on tick populations. Gilbert and colleagues [176] have shown in Scotland that *I*. *ricinus* tick populations are smaller in forests or heathlands where hunting pressure is higher, and that, 4 to 5 years after the fencing of experimental sites, tick populations are less abundant. More dramatically, Rand and colleagues [177] showed that the removal of white-tailed deer (*Odocoileus virginianus*) from an island on the East Coast of the United States—where no other wild species is known to potentially host adult ticks—resulted in an increase in questing adult *I*. *scapularis* in the year following eradication of their preferred host, but a drastic drop in all stages in later years. However, the effect of reducing host populations in areas where host movements are not controlled is more nuanced [178]. For example, controlling *I*. *ricinus* tick populations by excluding deer appears to be effective in protecting the human population in specific areas [179], but excluding white-tailed deer to limit the abundance of *A*. *americanum* varies in effectiveness across different years [180].

Regarding *Hyalomma*, a study in Spain comparing an open and a closed area from which deer and wild boar had been excluded for 16 years showed that *H*. *lusitanicum* populations were more abundant in the open areas [181]. In a theoretical study based on a population dynamics model, it was shown that the decrease in density of hares, which host the immature stages of *H*. *marginatum*, is associated with a decrease in adult tick populations after 5 years of simulation [182]. Furthermore, studies have shown that under certain conditions in environments with relatively low host biodiversity, tick abundances in the environment are higher compared with environments harboring higher biodiversity. In environments with high biodiversity, the probability of encounter between ticks and their preferred host is reduced and feeding success is lower due to grooming behavior or resistance to ticks of some of the hosts present. For example, in the United States, *I*. *scapularis* feeds on a wide variety of hosts [183]. In addition to the species richness of environments, functional diversity is also important, in particular, the presence of predators that may limit host populations or limit the foraging time of these hosts (and thus potential contact with exophilic ticks) [184,185]. To our knowledge, no such studies have been conducted on *Hyalomma* ticks.

For tick species that feed on livestock, rotational grazing may reduce host infestation by removing animals from a pasture plot for the duration necessary for the free-living ticks present there to die out by starvation [75,186]. This practice is particularly suitable if animals are treated with an acaricide at each change of pasture plot, thus avoiding immediate reinfestation of the pasture by the engorged ticks introduced by the animal host. However, this strategy can only be effective for species in which the survival time of the free-living stages in the environment is not very long, such as for the larvae of *R*. *microplus*, a monophasic tick. This strategy is not possible with 2- or 3-host ticks such as *Hyalomma* spp. whose unfed adults can survive on pasture lands for several years under good conditions [187]. For the rotation system to work, there must also be no alternative hosts in the environment that allow the cycle to be completed in the absence of the domestic host. In some cases, this would require a hermetic fence around the pastures, which is very rarely possible.

For ticks feeding on domestic animals, it is also possible to adapt herd management to the tick activity cycle, but data are lacking for *Hyalomma* spp. Knowledge of their rhythm of detachment at repletion could, for example, theoretically make it possible to favor detachment in places that are unsuitable for their survival or oviposition. For example, as engorged *R. microplus* females detach mainly in the morning, holding animals in the morning, before grazing, in night pens or stables where the detached engorged females will not survive, can thus limit the infestation of the environment [188]. In contrast, as engorged *A. variegatum* nymphs detach from the host in the afternoon (2 PM to 5:30 PM), if the herds are kept during this period on pastures unfavorable to tick survival, or on plots subsequently cultivated, it can greatly reduce adult tick infestation in the following months [189]. Similarly, noting that *A. variegatum* adults are more active during the day than at night, Barré (1998) suggested to encourage the nocturnal grazing of cattle. However, these actions are limited by their feasibility in terms of herd management as well as by the plasticity of tick behavior that can adapt to their environment [190].

Finally, manual tick removal of domestic animal hosts is also used by farmers in smallholdings [191]. This operation mainly targets adult ticks, because larvae and nymphs are difficult to detect, and can secondarily reduce tick densities in pastures. However, the risk of infection must be controlled when handling ticks.

The difficulty with all these control methods lies, among other things, in understanding and taking into account their short- and long-term ecological consequences. On the one hand, the effects observed on the short term are not necessarily those observed on the long term and, on the other hand, the ecological consequences on the ecosystem as a whole are difficult to predict due to the evolution of community dynamics.

Other avenues of research

Recent advances in the description and study of the tick microbiome (see review [192]) open up new avenues of research to identify strategies for tick control. For example, studies of mosquito vectors have shown that modulating their microbiome reduces the transmission of pathogens responsible for malaria, dengue, and other mosquito-associated diseases [193]. Using their own microbiome as a "weapon" against ticks can be seen from 2 different angles. One approach is to target microbes that are necessary for tick survival or development, such as those responsible for nutrient supplementation or stress reduction; vaccination against *I. ricinus* is based on these tick microbes [194]. Another tack is to target components of the tick microbiome that are directly involved in pathogen transmission, by activating or suppressing the immune system, competition for limited resources or regulation of a specific physiological process. One example is the introduction of a vertically transmitted endosymbiont capable of inhibiting pathogen transmission into a laboratory tick population for release into the field to overtake natural populations. Additionally, based on the positive associations between the microbiome and certain tick-borne pathogens, vaccination strategies against these microbiome components may merit development. Clearly, it is now essential to study and understand the functional consequences of interactions between ticks, their microbiome, and pathogens, as in the study of the transmission of *B. burgdorferi* or *A. phagocytophilum* in *I. scapularis* to identify potential vaccine targets [194,195].

Although attractive, this approach to manipulating the microbiome will face a number of challenges that need to be addressed, in addition to the lack of functional data at present. Firstly, the dynamics of the tick microbiome vary not only between species, but also between geographical origin, sex, stage, or blood meal origin [192]. Therefore, these factors will have to be taken into account because they can represent important obstacles to the identification of a common usable target. Secondly, the release of ticks with a genetically modified microbiome into the field will come up against the same difficulties as those mentioned for genetic tick control methods (ethical and regulatory problems, low dispersion, long generation times, etc.).

Thirdly, as mentioned above with regard to anti-tick vaccines, it should also be kept in mind that a vaccine approach directed against elements of the microbiome will be complex to implement for multi-host ticks. Compared with other genera, relatively little work has been done on the *Hyalomma* microbiome [196–199]. However, a recent study has demonstrated, using tick samples collected in the field in Pakistan, that populations of *Francisella*-like endosymbionts and *Candidatus* Midichloria mitochondrii, which predominate in female *H. anatolicum*, are not altered by the presence of 2 pathogens they transmit: *Theileria* sp. and *A. marginale* [200].

Finally, new approaches based on existing, but more environmentally friendly strategies can also be considered in tick control. One example is the very recent development of a pheromone trap which, after attracting *R. sanguineus* ticks, kills them by electrocution [201]. This type of trap, which to our knowledge has never been tested on *Hyalomma* sp., could prove effective due to the hunting behavior of adults. The identification of new tick-specific targets, such as substances in their nervous system, may also allow the development of vaccines [202] or new acaricides that preserve non-target fauna [203], particularly in association with nanoparticles [58].

Conclusion

As with other tick species and genera, there is currently no "miracle solution" for controlling *Hyalomma* spp. According to the danger they represent, whether in terms of transmission of the CCHF virus to humans or of parasites such as *Theileria* sp. to animals, it is now urgent to develop new methods of control that are environmentally sustainable against these very important disease vectors, especially considering current global changes and the growing resistance to acaricides. In that context, an attractive approach for preventing tick-borne diseases can consist of development of vaccines that target conserved tick molecules as it may provide broad protection against current and future tick-borne pathogens. However, it must be kept in mind that these methods must be adapted not only to the biology and ecology of the species involved, for which much data are still lacking, but also to the realities of the field, taking into account the feasibility of their application, as well as the expectations and acceptability of stakeholders and civil society. It is only with the compliance of the relevant populations and within the framework of an integrated control plan aimed at changing practices (breeding, human activities in risk areas, etc.) that solutions to fight ticks, including *Hyalomma* spp., can be implemented.

Key Learning Points

- *Hyalomma* spp. ticks are responsible of negative impact both directly due to their bite because they are some ectoparasites and indirectly as important disease vectors for humans and animals.
- The geographic distribution of *Hyalomma* ticks is currently expanding due to global changes, suggesting the possibility of emerging diseases related to these vectors.
- In the absence of vaccine and specific treatment against Crimean hemorrhagic fever (CCHF) virus transmitted by *Hyalomma* sp., the only control method available at present is the control of tick vectors.

- Integrated pest management combining several approaches adapted to the local context and species is currently the best strategy for tick control together with a rational use of acaricide.
- Continued efforts are needed to develop and implement new and innovative methods of tick control.

Top Five Papers

1. Gray JS, Dautel H, Estrada-Pena A, Kahl O, Lindgren E. Effects of climate change on ticks and tick-borne diseases in europe. Interdisciplinary perspectives on infectious diseases. 2009;2009:593232.
2. Vial L, Stachurski F, Leblond A, Huber K, Vourc'h G, et al. Strong evidence for the presence of the tick Hyalomma marginatum Koch, 1844 in southern continental France. Ticks Tick Borne Dis. 2016;7:1162–1167.
3. Negredo A, Sanchez-Ledesma M, Llorente F, Perez-Olmeda M, Belhassen-Garcia M, et al. Retrospective Identification of Early Autochthonous Case of Crimean-Congo Hemorrhagic Fever, Spain, 2013. Emerg Infect Dis. 2021;27:1754–1756.
4. Bakheit M, Latif A, Vatansever Z, Seitzer U, Ahmed J. The Huge Risks Due to *Hyalomma* Ticks. In: Mehlhorn H, editor. Arthropods as vectors of emerging diseases. New York: Springer; 2012. p. 167–194.
5. Graf JF, Gogolewski R, Leach-Bing N, Sabatini GA, Molento MB, et al. Tick control: an industry point of view. Parasitology. 2004;(129 Suppl): S427-442.

Acknowledgments

This review was conducted by the ad hoc subgroup from the working expert group on the risks related to *Hyalomma* ticks at the French Agency for Food, Environmental and Occupational Health & Safety (ANSES) commissioned by the French authorities. The authors thank the other experts who were part of this group for stimulating discussions and for their feedback on the expert report: S. Baize, S. Bertagnoli, P. Marianneau, M. Rene-Martellet, F. Stachurski, and L. Vial.

References

1. de la Fuente J, Antunes S, Bonnet S, Cabezas-Cruz A, Domingos AG, Estrada-Pena A, et al. Tick-Pathogen Interactions and Vector Competence: Identification of Molecular Drivers for Tick-Borne Diseases. Front Cell Infect Microbiol. 2017; 7:114. https://doi.org/10.3389/fcimb.2017.00114 PMID: 28439499

2. de la Fuente J, Estrada-Pena A, Venzal JM, Kocan KM, Sonenshine DE. Overview: Ticks as vectors of pathogens that cause disease in humans and animals. Front Biosci. 2008; 13:6938–6946. https://doi.org/10.2741/3200 PMID: 18508706

3. Barre N, Uilenberg G. Spread of parasites transported with their hosts: case study of two species of cattle tick. Rev Sci Tech. 2010; 29(1):149–60–35–47. PMID: 20617654

4. Medlock JM, Hansford KM, Bormane A, Derdakova M, Estrada-Pena A, George JC, et al. Driving forces for changes in geographical distribution of *Ixodes ricinus* ticks in Europe. Parasit Vectors. 2013; 6:1. https://doi.org/10.1186/1756-3305-6-1 PMID: 23281838

5. Ogden NH. Climate change and vector-borne diseases of public health significance. FEMS Microbiol Lett. 2017; 364(19). https://doi.org/10.1093/femsle/fnx186 PMID: 28957457

6. Gray JS, Dautel H, Estrada-Pena A, Kahl O, Lindgren E. Effects of climate change on ticks and tick-borne diseases in europe. Interdiscip Perspect Infect Dis. 2009; 2009:593232. https://doi.org/10.1155/2009/593232 PMID: 19277106

7. Wikel SK. Ticks and Tick-Borne Infections: Complex Ecology, Agents, and Host Interactions. Vet Sci. 2018; 5(2).

8. Eisen RJ, Eisen L. The Blacklegged Tick, *Ixodes scapularis*: An Increasing Public Health Concern. Trends Parasitol. 2018; 34(4):295–309.

9. Stachurski F, Boulanger N, Blisnick A, Vial L, Bonnet S. Climate change alone cannot explain altered tick distribution across Europe: a spotlight on endemic and invasive tick species. In: Nuttall PA, editor. Climate, Ticks and Disease. UK: Cabi; 2021.

10. Kampen H, Poltz W, Hartelt K, Wolfel R, Faulde M. Detection of a questing *Hyalomma marginatum marginatum* adult female (Acari, Ixodidae) in southern Germany. Exp Appl Acarol. 2007; 43(3):227–231. https://doi.org/10.1007/s10493-007-9113-y PMID: 17952610

11. Uiterwijk M, Ibanez-Justicia A, van de Vossenberg B, Jacobs F, Overgaauw P, Nijsse R, et al. Imported *Hyalomma* ticks in the Netherlands 2018–2020. Parasit Vectors. 2021; 14(1):244. https://doi.org/10.1186/s13071-021-04738-x PMID: 33962655

12. Sormunen JJ, Klemola T, Vesterinen EJ. Ticks (Acari: Ixodidae) parasitizing migrating and local breeding birds in Finland. Exp Appl Acarol. 2021. https://doi.org/10.1007/s10493-021-00679-3 PMID: 34787774

13. Vial L, Stachurski F, Leblond A, Huber K, Vourc'h G, Rene-Martellet M, et al. Strong evidence for the presence of the tick Hyalomma marginatum Koch, 1844 in southern continental France. Ticks Tick Borne Dis. 2016; 7(6):1162–1167. https://doi.org/10.1016/j.ttbdis.2016.08.002 PMID: 27568169

14. Negredo A, Sanchez-Ledesma M, Llorente F, Perez-Olmeda M, Belhassen-Garcia M, Gonzalez-Calle D, et al. Retrospective Identification of Early Autochthonous Case of Crimean-Congo Hemorrhagic Fever, Spain, 2013. Emerg Infect Dis. 2021; 27(6):1754–1756. https://doi.org/10.3201/eid2706.204643 PMID: 34013861

15. Guglielmone A, Robbins R, Apanaskevich D, Petney T, Estrada-Pena A, Horak I, et al. The *Argasidae*, Ixodidae and *Nuttalliellidae* (Acari: Ixodida of the world: a list of valid species names. Zootaxa. 2010; 2528:1–28.

16. Estrada-Pena A, Jongejan F. Ticks feeding on humans: a review of records on human-biting Ixodoidea with special reference to pathogen transmission. Exp Appl Acarol. 1999; 23(9):685–715. https://doi.org/10.1023/a:1006241108739 PMID: 10581710

17. Kar S, Rodriguez SE, Akyildiz G, Cajimat MNB, Bircan R, Mears MC, et al. Crimean-Congo hemorrhagic fever virus in tortoises and *Hyalomma aegyptium* ticks in East Thrace, Turkey: potential of a cryptic transmission cycle. Parasit Vectors. 2020; 13(1):201. https://doi.org/10.1186/s13071-020-04074-6 PMID: 32307010

18. Apanaskevich D, Oliver J. Life cycles and natural history of ticks. In: Sonenshine DE, Roe RM, editors. Biology of ticks. 1. NewYork, USA: Oxford University Press; 2014. p. 59–73.

19. Bakheit M, Latif A, Vatansever Z, Seitzer U, Ahmed J. The Huge Risks Due to *Hyalomma* Ticks. In: Mehlhorn H, editor. Arthropods as vectors of emerging diseases. New York: Springer; 2012. p. 167–94.

20. Gargili A, Estrada-Pena A, Spengler JR, Lukashev A, Nuttall PA, Bente DA. The role of ticks in the maintenance and transmission of Crimean-Congo hemorrhagic fever virus: A review of published field and laboratory studies. Antiviral Res. 2017; 144:93–119. https://doi.org/10.1016/j.antiviral.2017.05.010 PMID: 28579441

21. Okorie TG, Fabiyi A. The multiplication of Dugbe virus in the Ixodid tick, *Hyalomma rufipes* Koch, after experimental infection. Tropenmed Parasitol. 1979; 30(4):439–442.

22. Formosinho P, Santos-Silva MM. Experimental infection of *Hyalomma marginatum* ticks with West Nile virus. Acta Virol. 2006; 50(3):175–180.

23. Linthicum KJ, Logan TM. Weight gain, hemoglobin uptake, and virus ingestion by *Hyalomma truncatum* (Acari: *Ixodidae*) ticks after engorgement on viremic guinea pigs. J Med Entomol. 1994; 31(2):306–309. https://doi.org/10.1093/jmedent/31.2.306 PMID: 8189423

24. Awad FI, Amin MM, Salama SA, Khide S. The role played by *Hyalomma dromedarii* in the transmission of African horse sickness virus in Egypt. Bull Anim Health Prod Afr. 1981; 29(4):337–340. PMID: 7348587
25. Singh KR, Bhatt PN. Transmission of Kyasanur Forest disease virus by *Hyalomma marginatum isaaci*. Indian J Med Res. 1968; 56(4):610–613.
26. Orkun O. Molecular investigation of the natural transovarial transmission of tick-borne pathogens in Turkey. Vet Parasitol. 2019; 273:97–104. https://doi.org/10.1016/j.vetpar.2019.08.013 PMID: 31473450
27. Shkap V, Kocan K, Molad T, Mazuz M, Leibovich B, Krigel Y, et al. Experimental transmission of field *Anaplasma marginale* and the *A. centrale* vaccine strain by *Hyalomma excavatum*, *Rhipicephalus sanguineus* and *Rhipicephalus (Boophilus) annulatus* ticks. Vet Microbiol. 2009; 134(3–4):254–260. https://doi.org/10.1016/j.vetmic.2008.08.004 PMID: 18823724
28. Pandurov S, Zaprianov M. Studies on the retention of *R. burneti* in *Rh. bursa* and *H. detritum* ticks. Vet Med Nauki. 1975; 12(4):43–48.
29. Siroky P, Kubelova M, Modry D, Erhart J, Literak I, Spitalska E, et al. Tortoise tick *Hyalomma aegyptium* as long term carrier of Q fever agent *Coxiella burnetii*—evidence from experimental infection. Parasitol Res. 2010; 107(6):1515–1520.
30. Agina OA, Shaari MR, Isa NMM, Ajat M, Zamri-Saad M, Hamzah H. Clinical Pathology, Immunopathology and Advanced Vaccine Technology in Bovine Theileriosis: A Review. Pathogens. 2020; 9(9):697. https://doi.org/10.3390/pathogens9090697 PMID: 32854179
31. Ros-Garcia A, M'Ghirbi Y, Bouattour A, Hurtado A. First detection of *Babesia occultans* in *Hyalomma* ticks from Tunisia. Parasitology. 2011; 138(5):578–582.
32. Altay K, Aktas M, Dumanli N. *Theileria* infections in small ruminants in the east and southeast Anatolia. Turkiye Parazitol Derg. 2007; 31(4):268–271. PMID: 18224614
33. Ghafar A, Abbas T, Rehman A, Sandhu ZU, Cabezas-Cruz A, Jabbar A. Systematic Review of Ticks and Tick-Borne Pathogens of Small Ruminants in Pakistan. Pathogens. 2020; 9(11). https://doi.org/10.3390/pathogens9110937 PMID: 33187238
34. Nadal C, Bonnet SI, Marsot M. Eco-epidemiology of equine piroplasmosis and its associated tick vectors in Europe: A systematic literature review and a meta-analysis of prevalence. Transbound Emerg Dis. 2021.
35. De Waal DT. The transovarial transmission of *Babesia caballi* by *Hyalomma truncatum*. Onderstepoort J Vet Res. 1990; 57(1):99–100.
36. Jongejan F, Uilenberg G. Ticks and control methods. Rev Sci Tech. 1994; 13(4):1201–1226. https://doi.org/10.20506/rst.13.4.818 PMID: 7711310
37. Walker AR, Bouattour A, Camicas J-L, Estrada-Peña A, Horak IG, Latif AA, et al. Ticks of Domestic Animals in Africa: a guide to identification of species. Edinburgh Scotland, UK: Bioscience Reports; 2014.
38. Angus BM. The history of the cattle tick *Boophilus microplus* in Australia and achievements in its control. Int J Parasitol. 1996; 26(12):1341–1355.
39. Gharbi M, Darghouth MA. A review of Hyalomma scupense (Acari, Ixodidae) in the Maghreb region: from biology to control. Parasite. 2014; 21:2. https://doi.org/10.1051/parasite/2014002 PMID: 24507485
40. Mehlhorn H, Schumacher B, Jatzlau A, Abdel-Ghaffar F, Al-Rasheid KA, Klimpel S, et al. Efficacy of deltamethrin (Butox(R) 7.5 pour on) against nymphs and adults of ticks (*Ixodes ricinus, Rhipicephalus sanguineus*) in treated hair of cattle and sheep. Parasitol Res. 2011; 108(4):963–971.
41. Prullage JB, Tran HV, Timmons P, Harriman J, Chester ST, Powell K. The combined mode of action of fipronil and amitraz on the motility of *Rhipicephalus sanguineus*. Vet Parasitol. 2011; 179(4):302–310.
42. de Oliveira PR, Calligaris IB, Nunes PH, Bechara GH, Camargo-Mathias MI. Fluazuron-induced morphological changes in *Rhipicephalus sanguineus* Latreille, 1806 (Acari: *Ixodidae*) nymphs: An ultrastructural evaluation of the cuticle formation and digestive processes. Acta Trop. 2014; 133:45–55. PMID: 24508101
43. Giles MB. Ivermectin in tick control. Vet Rec. 1986; 118(3):82. https://doi.org/10.1136/vr.118.3.82-b PMID: 3754075
44. Graf JF, Gogolewski R, Leach-Bing N, Sabatini GA, Molento MB, Bordin EL, et al. Tick control: an industry point of view. Parasitology. 2004; 129(Suppl):S427–S442. https://doi.org/10.1017/s0031182004006079 PMID: 15938522
45. Sajid MS, Iqbal Z, Khan MN, Muhammad G. In vitro and in vivo efficacies of ivermectin and cypermethrin against the cattle tick *Hyalomma anatolicum anatolicum* (Acari: *Ixodidae*). Parasitol Res. 2009; 105(4):1133–1138. https://doi.org/10.1007/s00436-009-1538-2 PMID: 19562374

46. Kamran K, Ali A, Villagra CA, Bazai ZA, Iqbal A, Sajid MS. *Hyalomma anatolicum* resistance against ivermectin and fipronil is associated with indiscriminate use of acaricides in southwestern Balochistan. Pakistan Parasitol Res. 2021; 120(1):15–25.

47. Gaur RS, Sangwan AK, Sangwan N, Kumar S. Acaricide resistance in *Rhipicephalus (Boophilus) microplus* and *Hyalomma anatolicum* collected from Haryana and Rajasthan states of India. Exp Appl Acarol. 2016; 69(4):487–500. https://doi.org/10.1007/s10493-016-0046-1 PMID: 27100113

48. Singh NK, Gelot IS, Jyoti BSA, Singh H, Singh V. Detection of acaricidal resistance in *Hyalomma anatolicum anatolicum* from Banaskantha district. Gujarat J Parasit Dis. 2015; 39(3):563–566.

49. Shyma KP, Kumar S, Sharma AK, Ray DD, Ghosh S. Acaricide resistance status in Indian isolates of *Hyalomma anatolicum*. Exp Appl Acarol. 2012; 58(4):471–481.

50. Lu H, Ren Q, Li Y, Liu J, Niu Q, Yin H, et al. The efficacies of 5 insecticides against hard ticks *Hyalomma asiaticum*, *Haemaphysalis longicornis* and *Rhipicephalus sanguineus*. Exp Parasitol. 2015; 157:44–47.

51. el-Azazy OM. Camel tick (Acari:Ixodidae) control with pour-on application of flumethrin. Vet Parasitol. 1996; 67(3–4):281–284. https://doi.org/10.1016/s0304-4017(96)00938-7 PMID: 9017876

52. Van Der Merwe JS, Smit FJ, Durand AM, Kruger LP, Michael LM. Acaricide efficiency of amitraz/cypermethrin and abamectin pour-on preparations in game. Onderstepoort J Vet Res. 2005; 72 (4):309–314. https://doi.org/10.4102/ojvr.v72i4.187 PMID: 16562734

53. Ghosh S, Azhahianambi P, Yadav MP. Upcoming and future strategies of tick control: a review. J Vector Borne Dis. 2007; 44(2):79–89. PMID: 17722860

54. Salman M, Abbas RZ, Israr M, Abbas A, Mehmood K, Khan MK, et al. Repellent and acaricidal activity of essential oils and their components against *Rhipicephalus* ticks in cattle. Vet Parasitol. 2020; 283:109178.

55. Banumathi B, Vaseeharan B, Rajasekar P, Prabhu NM, Ramasamy P, Murugan K, et al. Exploitation of chemical, herbal and nanoformulated acaricides to control the cattle tick, *Rhipicephalus (Boophilus) microplus—A* review. Vet Parasitol. 2017; 244:102–110. https://doi.org/10.1016/j.vetpar.2017.07.021 PMID: 28917299

56. Regassa A. The use of herbal preparations for tick control in western Ethiopia. J S Afr Vet Assoc. 2000; 71(4):240–243. https://doi.org/10.4102/jsava.v71i4.722 PMID: 11212935

57. Kumar B, Manjunathachar HV, Ghosh S. A review on *Hyalomma* species infestations on human and animals and progress on management strategies. Heliyon. 2020; 6(12):e05675.

58. Benelli G, Maggi F, Romano D, Stefanini C, Vaseeharan B, Kumar S, et al. Nanoparticles as effective acaricides against ticks-A review. Ticks Tick Borne Dis. 2017; 8(6):821–826. https://doi.org/10.1016/j.ttbdis.2017.08.004 PMID: 28865955

59. Sonenshine DE, Adams T, Allan SA, McLaughlin J, Webster FX. Chemical composition of some components of the arrestment pheromone of the black-legged tick, *Ixodes scapularis* (Acari: *Ixodidae*) and their use in tick control. J Med Entomol. 2003; 40(6):849–859. https://doi.org/10.1603/0022-2585-40.6.849 PMID: 14765662

60. Allan SA, Norval RA, Sonenshine DE, Burridge MJ. Efficacy of tail-tag decoys impregnated with pheromone and acaricide for control of bont ticks on cattle. Ann N Y Acad Sci. 1996; 791:85–93. https://doi.org/10.1111/j.1749-6632.1996.tb53514.x PMID: 8784489

61. Kelly PJ, Lucas HM, Randolph CM, Ackerson K, Blackburn JK, Dark MJ. Efficacy of slow-release tags impregnated with aggregation-attachment pheromone and deltamethrin for control of *Amblyomma variegatum* on St. Kitts, West Indies. Parasit Vectors. 2014; 7:182. https://doi.org/10.1186/1756-3305-7-182 PMID: 24731252

62. Norval R, Butler J, Yunker C. Use of carbon dioxide and natural or synthetic aggregation-attachment pheromone of the bont tick, *Amblyomma hebraeum*, to attract and trap unfed adults in the field. Exp Appl Acarol. 1989; 7:171–180.

63. Barre N, Garris GI, Lorvelec O. Field sampling of the tick *Amblyomma variegatum* (Acari: *Ixodidae*) on pastures in Guadeloupe; attraction of CO2 and/or tick pheromones and conditions of use. Exp Appl Acarol. 1997; 21(2):95–108. https://doi.org/10.1023/b:appa.0000031788.88306.77 PMID: 9080680

64. Greeshma Rao U, Narladkar B. Role of entomopathogenic fungi in tick control: A Review. J Entomol Zool Stud. 2018; 6(1):1265–1269.

65. Beys-da-Silva WO, Rosa RL, Berger M, Coutinho-Rodrigues CJB, Vainstein MH, Schrank A, et al. Updating the application of *Metarhizium anisopliae* to control cattle tick *Rhipicephalus microplus* (Acari: *Ixodidae*). Exp Parasitol. 2020; 208:107812. https://doi.org/10.1016/j.exppara.2019.107812 PMID: 31809704

66. Stafford KC 3rd, Allan SA. Field applications of entomopathogenic fungi *Beauveria bassiana* and *Metarhizium anisopliae* F52 (*Hypocreales: Clavicipitaceae*) for the control of *Ixodes scapularis* (Acari:

Ixodidae). J Med Entomol. 2010; 47(6):1107–1115. https://doi.org/10.1603/me10019 PMID: 21175060

67. Samish M, Alekseev E, Glazer I. Biocontrol of ticks by entomopathogenic nematodes. Research update. Ann N Y Acad Sci. 2000; 916:589–594. https://doi.org/10.1111/j.1749-6632.2000.tb05341.x PMID: 11193678

68. Lormendez CC, Fernandez-Ruvalcaba M, Adames-Mancebo M, Hernandez-Velazquez VM, Zuniga-Navarrete F, Flores-Ramirez G, et al. Mass production of a S-layer protein of *Bacillus thuringiensis* and its toxicity to the cattle tick *Rhipicephalus microplus*. Sci Rep. 2019; 9(1):17586. https://doi.org/10.1038/s41598-019-53854-3 PMID: 31772196

69. Cuisance D, Barré N, De Deken R. (Ectoparasites des animaux: méthodes de lutte écologique, biologique, génétique et mécanique. Revue scientifique et technique de l'Office international des Epizooties.) In French. Revue scientifique et technique de l'Office international des Epizooties. 1994; 13 (4):1305–1356.

70. Mwangi EN, Hassan SM, Kaaya GP, Essuman S. The impact of *Ixodiphagus hookeri*, a tick parasitoid, on *Amblyomma variegatum* (Acari: *Ixodidae*) in a field trial in Kenya. Exp Appl Acarol. 1997; 21 (2):117–126. https://doi.org/10.1023/b:appa.0000031790.30821.57 PMID: 9080682

71. Krawczyk AI, Bakker JW, Koenraadt CJM, Fonville M, Takumi K, Sprong H, et al. Tripartite Interactions among I*xodiphagus hookeri, Ixodes ricinus* and Deer: Differential Interference with Transmission Cycles of Tick-Borne Pathogens. Pathogens. 2020; 9(5). https://doi.org/10.3390/pathogens9050339 PMID: 32365910

72. Stutterheim IM, Bezuidenhout JD, Elliott EG. Comparative feeding behaviour and food preferences of oxpeckers (*Buphagus erythrorhynchus* and *B. africanus*) in captivity. Onderstepoort J Vet Res. 1988; 55(3):173–179. PMID: 3194119

73. Hassan SM, Dipeolu OO, Amoo AO, Odhiambo TR. Predation on livestock ticks by chickens. Vet Parasitol. 1991; 38(2–3):199–204. https://doi.org/10.1016/0304-4017(91)90129-j PMID: 1858289

74. Dreyer K, Fourie LJ, Kok DJ. Predation of livestock ticks by chickens as a tick-control method in a resource-poor urban environment. Onderstepoort J Vet Res. 1997; 64(4):273–276. PMID: 9551478

75. Wilkinson P. Factors affecting the distribution and abundance of the cattle tick in Australia: observations and hypotheses. Acarologia. 1970; 3:492–508.

76. Petney TN, Horak IG, Rechav Y. The ecology of the African vectors of heartwater, with particular reference to *Amblyomma hebraeum* and *Amblyomma variegatum*. Onderstepoort J Vet Res. 1987; 54 (3):381–395.

77. Burns EC, Melancon DG. Effect of imported fire ant (*Hymenoptera: Formicidae*) invasion on lone star tick (Acarina: *Ixodidae*) populations. J Med Entomol. 1977; 14(2):247–249. https://doi.org/10.1093/jmedent/14.2.247 PMID: 606827

78. Butler J, Camino M, Perez T. *Boophilus microplus* and the fire ant *Solenopsis geminata*. Recent Advances in Acarology. 1979; 1:469–472.

79. Barre N, Mauleon H, Garris GI, Kermarrec A. Predators of the tick *Amblyomma variegatum* (Acari: *Ixodidae*) in Guadeloupe. French West Indies Exp Appl Acarol. 1991; 12(3–4):163–170.

80. Stachurski F, Zoungrana S, Konkobo M. Moulting and survival of *Amblyomma variegatum* (Acari: *Ixodidae*) nymphs in quasi-natural conditions in Burkina Faso; tick predators as an important limiting factor. Exp Appl Acarol. 2010; 52(4):363–376. https://doi.org/10.1007/s10493-010-9370-z PMID: 20593224

81. Gonzalez J, Valcarcel F, Perez-Sanchez JL, Tercero-Jaime JM, Cutuli MT, Olmeda AS. Control of *Hyalomma lusitanicum* (Acari: *Ixodidade*) Ticks Infesting Oryctolagus cuniculus (Lagomorpha: Leporidae) Using the Entomopathogenic Fungus *Beauveria bassiana* (Hyocreales: *Clavicipitaceae*) in Field Conditions. J Med Entomol. 2016; 53(6):1396–1402. https://doi.org/10.1093/jme/tjw088 PMID: 27297213

82. Sun M, Ren Q, Liu Z, Guan G, Gou H, Ma M, et al. *Beauveria bassiana*: Synergistic effect with acaricides against the tick *Hyalomma anatolicum anatolicum* (Acari: Ixodidae). Exp Parasitol. 2011; 128 (3):192–195. https://doi.org/10.1016/j.exppara.2011.03.012 PMID: 21440547

83. Suleiman EA, Shigidi MT, Hassan SM. *Metarhizium anisopliae* as a biological control agent against *Hyalomma anatolicum* (Acari: Ixodidae). Pak J Biol Sci. 2013; 16(24):1943–1949. https://doi.org/10.3923/pjbs.2013.1943.1949 PMID: 24517010

84. Suleiman E, Shigidi M, Hussan S. Activity of *Scopulariopsis brevicaulis* on *Hyalomma anatolicum* and *Amblyomma lepidum* (acari: ixodidae). J Med Sci. 2013; 13:667–675.

85. Habeeb SM, Ashry HM, Saad MM. Ovicidal effect of chitinase and protease enzymes produced by soil fungi on the camel tick *Hyalomma dromedarii* eggs (Acari:*Ixodidae*). J Parasit Dis. 2017; 41(1):268–273. https://doi.org/10.1007/s12639-016-0791-4 PMID: 28316424

86. Samish M, Alekseev E, Glazer I. Interaction between ticks (Acari: Ixodidae) and pathogenic nematodes (Nematoda): susceptibility of tick species at various developmental stages. J Med Entomol. 1999; 36(6):733–740. https://doi.org/10.1093/jmedent/36.6.733 PMID: 10593074

87. Samish M, Alekseev E, Glazer I. Mortality rate of adult ticks due to infection by entomopathogenic nematodes. J Parasitol. 2000; 86(4):679–684. https://doi.org/10.1645/0022-3395(2000)086[0679:MROATD]2.0.CO;2 PMID: 10958439

88. El-Sadawy HA, Zayed AA, El-Shazly A. Characterization of midgut and salivary gland proteins of *Hyalomma dromedarii* females controlled by entomopathogenic nematodes. Pak J Biol Sci. 2008; 11 (4):508–516.

89. Habeeb SM, El-Hag HAA. Ultrastructural changes in hemocyte cells of hard tick (*Hyalomma dromedarii: Ixodidae*): a model of *Bacillus thuringiensis var. Thuringiensis* H14 *-endotoxin mode of action. J Agric Environ Sci. 2008; 6:829–836.

90. Samish M, Rehacek J. Pathogens and predators of ticks and their potential in biological control. Annu Rev Entomol. 1999; 44:159–182. https://doi.org/10.1146/annurev.ento.44.1.159 PMID: 9990719

91. Sharma A, Pham MN, Reyes JB, Chana R, Yim WC, Heu CC, et al. Cas9-mediated gene editing in the black-legged tick, Ixodes scapularis, by embryo injection and ReMOT Control. iScience. 2022; 25 (3):103781. https://doi.org/10.1016/j.isci.2022.103781 PMID: 35535206

92. Bonnet SI, Blisnick T, Al Khoury C, Guillot J. Of fungi and ticks: Morphological and molecular characterization of fungal contaminants of a laboratory-reared Ixodes ricinus colony. Ticks Tick Borne Dis. 2021; 12(5):101732. https://doi.org/10.1016/j.ttbdis.2021.101732 PMID: 33992909

93. Srivastava PS, Sharma NN. Effects of 60Co irradiation on unfed adults and engorged females of the tick *Hyalomma anatolicum*. Int J Radiat Biol Relat Stud Phys Chem Med. 1976; 29(3):241–248.

94. Karaer Z, Kar S, Duzgun A, Guven E, Cakmak A, Emre Z, et al. Comparison of the ability to fertilize females by *Hyalomma anatolicum anatolicum* males irradiated with gamma radiation from caesium 137 with non-irradiated males. Turkiye Parazitol Derg. 2009; 33(1):37–42.

95. Karaer Z, Kar S, Duzgun A, Guven E, Pekmezci Z, Emre Z. The importance of gamma irradiations with caesium-137 for *Hyalomma anatolicum anatolicum* (Metastigmata, *Ixodidae*) control. Turkiye Parazitol Derg. 2006; 30(4):322–326.

96. Karaer Z, Güven E, Kar S. Examination of competitiveness of irradiated (Caesium-137) *Hyalomma marginatum* males in copulation. Kafkas Univ Vet Fak Derg. 2010; 16:497–501.

97. Bakirci S, Bilgiç H, Karaer Z, Düzgün A, Emre Z. Studies on the application of the sterile-male technique on the tick *Hyalomma excavatum*. Ankara Üniv Vet Fak Derg. 2013; 60:93–98.

98. de la Fuente J, Almazan C, Naranjo V, Blouin EF, Meyer JM, Kocan KM. Autocidal control of ticks by silencing of a single gene by RNA interference. Biochem Biophys Res Commun. 2006; 344(1):332–338. https://doi.org/10.1016/j.bbrc.2006.03.109 PMID: 16630571

99. Burrow H, Mans B, Cardoso F, Birkett M, Kotze A, Hayes B, et al. Towards a new phenotype for tick resistance in beef anddairy cattle: a review. Anim Prod Sci. 2019; 59:1401–1427.

100. Barnard DR. Population growth rates for *Amblyomma americanum* (Acari: *Ixodidae*) on *Bos indicus, B. taurus* and *B. indicus x B. taurus* cattle. Exp Appl Acarol. 1990; 9(3–4):259–265. https://doi.org/10.1007/BF01193432 PMID: 2261818

101. Hewetson RW. The inheritance of resistance by cattle to cattle tick. Aust Vet J. 1972; 48(5):299–303. https://doi.org/10.1111/j.1751-0813.1972.tb05161.x PMID: 5068812

102. Kongsuwan K, Piper EK, Bagnall NH, Ryan K, Moolhuijzen P, Bellgard M, et al. Identification of genes involved with tick infestation in *Bos taurus* and *Bos indicus*. Dev Biol (Basel). 2008; 132:77–88. https://doi.org/10.1159/000317146 PMID: 18817288

103. Maryam J, Babar ME, Nadeem A, Hussain T. Genetic variants in interferon gamma (IFN-gamma) gene are associated with resistance against ticks in *Bos taurus* and *Bos indicus*. Mol Biol Rep. 2012; 39(4):4565–4570.

104. Reason GK. Dairy cows with tick resistance: twenty years of the Australian Friesian Sahiwal [1983]. Qld Agric J. 2013; 109(3):135–138.

105. Hayman RH. The development of the Australian Milking Zebu. World Animal Rev. 1974; 11:31–35.

106. Utech KBW, Wharton RH. Breeding for resistance to *Boophilus microplus* in Australian Illawara Shorthorn and Brahman x Australian Illawara Shorthorn cattle. Aust Vet J. 1982; 58:41–46.

107. Seifert G. Selection of beef cattle in Northern Australia for resistance to the cattle tick (*Boophilus microplus*): Research and application. Prev Vet Med. 1984; 2:553–558.

108. Frisch JE, O'Neill CJ, Kelly MJ. Using genetics to control cattle parasites-the Rockhampton experience. Int J Parasitol. 2000; 30(3):253–264. https://doi.org/10.1016/s0020-7519(00)00010-2 PMID: 10719118

109. Stachurski F. Poor inheritance of low attractiveness for *Amblyomma variegatum* in cattle. Vet Parasitol. 2007; 146(3–4):321–328. https://doi.org/10.1016/j.vetpar.2007.02.025 PMID: 17418491

110. FAO. Report of the FAO expert consultation on revision of strategies for the control of ticks and tick-borne diseases. Rome: FAO; 1990.

111. Karasuyama H, Miyake K, Yoshikawa S. Immunobiology of Acquired Resistance to Ticks. Front Immunol. 2020; 11:601504. https://doi.org/10.3389/fimmu.2020.601504 PMID: 33154758

112. Jonsson NN, Piper EK, Constantinoiu CC. Host resistance in cattle to infestation with the cattle tick *Rhipicephalus microplus*. Parasite Immunol. 2014; 36(11):553–559.

113. Stachurski F. Variability of cattle infestation by *Amblyomma variegatum* and its possible utilisation for tick control. Rev Elev Med Vet Pays Trop. 1993; 46(1–2):341–348. PMID: 8134651

114. Rechav Y. Resistance of Brahman and Hereford cattle to African ticks with reference to serum gamma globulin levels and blood composition. Exp Appl Acarol. 1987; 3(3):219–232. https://doi.org/10.1007/BF01270458 PMID: 2456184

115. Spickett AM, De Klerk D, Enslin CB, Scholtz MM. Resistance of Nguni, Bonsmara and Hereford cattle to ticks in a Bushveld region of South Africa. Onderstepoort J Vet Res. 1989; 56(4):245–250. PMID: 2626263

116. Fourie LJ, Kok DJ, Heyne H. Adult ixodid ticks on two cattle breeds in the south-western Free State, and their seasonal dynamics. Onderstepoort J Vet Res. 1996; 63(1):19–23. PMID: 8848299

117. Gill HS, Walker AR. Differential cellular responses at *Hyalomma anatolicum anatolicum* feeding sites on susceptible and tick-resistant rabbits. Parasitology. 1985; 91(Pt 3):591–607.

118. Gill HS, Boid R, Ross CA. Isolation and characterization of salivary antigens from *Hyalomma anatolicum anatolicum*. Parasite Immunol. 1986; 8(1):11–25.

119. Gill HS, Luckins AG. *Hyalomma anatolicum anatolicum*: the role of humoral factors in the acquisition of host resistance. Exp Parasitol. 1987; 64(3):430–437.

120. Miranpuri GS. Relationship between the resistance of crossbred cattle to ticks, *Boophilus microplus* (Canestrini, 1887) and *Hyalomma anatolicum anatolicum* (Koch, 1844). Vet Parasitol. 1989; 31(3–4):289–301. https://doi.org/10.1016/0304-4017(89)90079-4 PMID: 2763448

121. Momin RR, Banerjee DP, Samantaray S. Attempted immunisation of crossbred calves (*Bos taurus x Bos indicus*) by repeated natural attachment of ticks *Hyalomma anatolicum anatolicum Koch* (1844). Tropl Anim Health Prod. 1991; 23(4):227–231.

122. Rechav Y, Dauth J, Els DA. Resistance of Brahman and Simmentaler cattle to southern African ticks. Onderstepoort J Vet Res. 1990; 57(1):7–12. PMID: 2339000

123. Mattioli RC, Dempfle L. Recent acquisitions on tick and tick-borne disease resistance in N'dama (*Bos taurus*) and Gobra zebu (*Bos indicus*) cattle. Parassitologia. 1995; 37(1):63–67. PMID: 8532370

124. Solomon G, Kaaya GP. Comparison of resistance in three breeds of cattle against African ixodid ticks. Exp Appl Acarol. 1996; 20(4):223–230. https://doi.org/10.1007/BF00054514 PMID: 8665816

125. Sahibi H, Rhalem A, Tikki N, Ben Kouka F, Barriga O. *Hyalomma* ticks: bovine resistance under field conditions as related to host age and breed. Parasite. 1997; 4(2):159–165. https://doi.org/10.1051/parasite/1997042159 PMID: 9296059

126. Narasimhan S, Kurokawa C, DeBlasio M, Matias J, Sajid A, Pal U, et al. Acquired tick resistance: The trail is hot. Parasite Immunol. 2020:e12808. https://doi.org/10.1111/pim.12808 PMID: 33187012

127. de la Fuente J, Contreras M. Additional considerations for anti-tick vaccine research. Expert Rev Vaccines. 2022; 21(8):1019–1021. https://doi.org/10.1080/14760584.2022.2071704 PMID: 35475778

128. Nuttall PA, Trimnell AR, Kazimirova M, Labuda M. Exposed and concealed antigens as vaccine targets for controlling ticks and tick-borne diseases. Parasite Immunol. 2006; 28(4):155–163. https://doi.org/10.1111/j.1365-3024.2006.00806.x PMID: 16542317

129. Rodriguez-Mallon A. Developing Anti-tick Vaccines. Methods Mol Biol. 2016; 1404:243–259. https://doi.org/10.1007/978-1-4939-3389-1_17 PMID: 27076303

130. Contreras M, Villar M, Alberdi P, de la Fuente J. Vaccinomics Approach to Tick Vaccine Development. Methods Mol Biol. 2016; 1404:275–286. https://doi.org/10.1007/978-1-4939-3389-1_19 PMID: 27076305

131. Valle MR, Guerrero FD. Anti-tick vaccines in the omics era. Front Biosci (Elite Ed). 2018; 10:122–136. https://doi.org/10.2741/e812 PMID: 28930608

132. Rego ROM, Trentelman JJA, Anguita J, Nijhof AM, Sprong H, Klempa B, et al. Counterattacking the tick bite: towards a rational design of anti-tick vaccines targeting pathogen transmission. Parasit Vectors. 2019; 12(1):229. https://doi.org/10.1186/s13071-019-3468-x PMID: 31088506

133. Bhowmick B, Han Q. Understanding Tick Biology and Its Implications in Anti-tick and Transmission Blocking Vaccines Against Tick-Borne Pathogens. Front Vet Sci. 2020; 7:319. https://doi.org/10.3389/fvets.2020.00319 PMID: 32582785

134. de la Fuente J, Estrada-Pena A. Why New Vaccines for the Control of Ectoparasite Vectors Have Not Been Registered and Commercialized? Vaccines (Basel). 2019; 7(3).

135. Rodriguez M, Penichet ML, Mouris AE, Labarta V, Luaces LL, Rubiera R, et al. Control of *Boophilus microplus* populations in grazing cattle vaccinated with a recombinant Bm86 antigen preparation. Vet Parasitol. 1995; 57(4):339–349.

136. Willadsen P, Bird P, Cobon GS, Hungerford J. Commercialisation of a recombinant vaccine against Boophilus microplus. Parasitology. 1995; 110(Suppl):S43–S50. https://doi.org/10.1017/s0031182000001487 PMID: 7784128

137. de la Fuente J, Rodriguez M, Montero C, Redondo M, Garcia-Garcia JC, Mendez L, et al. Vaccination against ticks (Boophilus spp.): the experience with the Bm86-based vaccine Gavac. Genet Anal. 1999; 15(3–5):143–148. https://doi.org/10.1016/s1050-3862(99)00018-2 PMID: 10596754

138. Kemp DH, Pearson RD, Gough JM, Willadsen P. Vaccination against Boophilus microplus: localization of antigens on tick gut cells and their interaction with the host immune system. Exp Appl Acarol. 1989; 7(1):43–58. https://doi.org/10.1007/BF01200452 PMID: 2667918

139. de la Fuente J, Almazan C, Canales M, Perez de la Lastra JM, Kocan KM, Willadsen P. A ten-year review of commercial vaccine performance for control of tick infestations on cattle. Anim Health Res Rev. 2007; 8(1):23–28. https://doi.org/10.1017/S1466252307001193 PMID: 17692140

140. de Vos S, Zeinstra L, Taoufik O, Willadsen P, Jongejan F. Evidence for the utility of the Bm86 antigen from *Boophilus microplus* in vaccination against other tick species. Exp Appl Acarol. 2001; 25(3):245–261.

141. Rodriguez-Valle M, Taoufik A, Valdes M, Montero C, Ibrahin H, Hassan SM, et al. Efficacy of *Rhipicephalus (Boophilus) microplus* Bm86 against *Hyalomma dromedarii* and *Amblyomma cajennense* tick infestations in camels and cattle. Vaccine. 2012; 30(23):3453–3458. https://doi.org/10.1016/j.vaccine.2012.03.020 PMID: 22446633

142. Contreras M, San Jose C, Estrada-Pena A, Talavera V, Rayas E, Isabel Leon C, et al. Control of tick infestations in wild roe deer (*Capreolus capreolus*) vaccinated with the Q38 Subolesin/Akirin chimera. Vaccine. 2020; 38(41):6450–6454. https://doi.org/10.1016/j.vaccine.2020.07.062 PMID: 32798140

143. Ben Said M, Galai Y, Mhadhbi M, Jedidi M, de la Fuente J, Darghouth MA. Molecular characterization of Bm86 gene orthologs from *Hyalomma excavatum*, *Hyalomma dromedarii* and *Hyalomma marginatum marginatum* and comparison with a vaccine candidate from *Hyalomma scupense*. Vet Parasitol. 2012; 190(1–2):230–240.

144. Jeyabal L, Azhahianambi P, Susitha K, Ray DD, Chaudhuri PV, Ghosh S. Efficacy of rHaa86, an Orthologue of Bm86, against challenge infestations of *Hyalomma anatolicum anatolicum*. Transbound Emerg Dis. 2010; 57(1–2):96–102. https://doi.org/10.1111/j.1865-1682.2010.01107.x PMID: 20537118

145. Azhahianambi P, De La Fuente J, Suryanarayana VV, Ghosh S. Cloning, expression and immunoprotective efficacy of rHaa86, the homologue of the Bm86 tick vaccine antigen, from *Hyalomma anatolicum anatolicum*. Parasite Immunol. 2009; 31(3):111–122.

146. Jeyabal L, Kumar B, Ray D, Azahahianambi P, Ghosh S. Vaccine potential of recombinant antigens of *Theileria annulata* and *Hyalomma anatolicum anatolicum* against vector and parasite. Vet Parasitol. 2012; 188(3–4):231–238.

147. Galai Y, Canales M, Ben Said M, Gharbi M, Mhadhbi M, Jedidi M, et al. Efficacy of *Hyalomma scupense* (Hd86) antigen against *Hyalomma excavatum* and *H. scupense* tick infestations in cattle. Vaccine. 2012; 30(49):7084–7089. https://doi.org/10.1016/j.vaccine.2012.09.051 PMID: 23036501

148. Ben Said M, Galai Y, Ben Ahmed M, Gharbi M, de la Fuente J, Jedidi M, et al. Hd86 mRNA expression profile in *Hyalomma scupense* life stages, could it contribute to explain anti-tick vaccine effect discrepancy between adult and immature instars? Vet Parasitol. 2013; 198(1–2):258–263. https://doi.org/10.1016/j.vetpar.2013.07.035 PMID: 24029714

149. Ben Said M, Galai Y, Canales M, Nijhof AM, Mhadhbi M, Jedidi M, et al. Hd86, the Bm86 tick protein ortholog in *Hyalomma scupense* (syn. *H. detritum*): expression in *Pichia pastoris* and analysis of nucleotides and amino acids sequences variations prior to vaccination trials. Vet Parasitol. 2012; 183(3–4):215–223. https://doi.org/10.1016/j.vetpar.2011.07.049 PMID: 21871736

150. Nijhof AM, Balk JA, Postigo M, Rhebergen AM, Taoufik A, Jongejan F. Bm86 homologues and novel ATAQ proteins with multiple epidermal growth factor (EGF)-like domains from hard and soft ticks. Int J Parasitol. 2010; 40(14):1587–1597. https://doi.org/10.1016/j.ijpara.2010.06.003 PMID: 20647015

151. Sangwan AK, Banerjee DP, Sangwan N. Immunization of cattle with nymphal *Hyalomma anatolicum anatolicum* extracts: Effects on tick biology. Tropl Anim Health Prod. 1998; 30(2):97–106.

152. Banerjee DP, Kumar R, Kumar S, Sengupta PP. Immunization of crossbred cattle (*Bos indicus x Bos taurus*) with fractionated midgut antigens against *Hyalomma anatolicum anatolicum*. Tropl Anim Health Prod. 2003; 35(6):509–19. https://doi.org/10.1023/a:1027325717124 PMID: 14690089

153. Banerjee DP, Momin RR, Samantaray S. Immunization of cattle (*Bos indicus X Bos taurus*) against *Hyalomma anatolicum anatolicum* using antigens derived from tick salivary gland extracts. Int J Parasitol. 1990; 20(7):969–972. https://doi.org/10.1016/0020-7519(90)90037-n PMID: 2276870

154. Sran HS, Grewal AS, Kondal JK. Enhanced immunity to *Hyalomma anatolicum anatolicum* ticks in cross-bred (*Bos indicus x Bos taurus*) calves using ascaris extract immunomodulator with the tick salivary gland extract antigens. Vet Immunol Immunopathol. 1996; 51(3–4):333–343. https://doi.org/10.1016/0165-2427(95)05517-7 PMID: 8792570

155. Das G, Ghosh S, Khan MH, Sharma JK. Immunization of cross-bred cattle against *Hyalomma anatolicum anatolicum* by purified antigens. Exp Appl Acarol. 2000; 24(8):645–659.

156. Das G, Ghosh S, Ray DD. Reduction of *Theileria annulata* infection in ticks fed on calves immunized with purified larval antigens of *Hyalomma anatolicum anatolicum*. Tropl Anim Health Prod. 2005; 37 (5):345–361. https://doi.org/10.1007/s11250-005-5080-7 PMID: 16274006

157. Ghosh S, Khan MH. Immunization of cattle against *Hyalomma anatolicum anatolicum* using larval antigens. Indian J Exp Biol. 1999; 37(2):203–205.

158. Sharma JK, Ghosh S, Khan MH, Das G. Immunoprotective efficacy of a purified 39 kDa nymphal antigen of *Hyalomma anatolicum anatolicum*. Tropl Anim Health Prod. 2001; 33(2):103–116. https://doi.org/10.1023/a:1005281429652 PMID: 11254071

159. Shakya M, Kumar B, Nagar G, de la Fuente J, Ghosh S. Subolesin: a candidate vaccine antigen for the control of cattle tick infestations in Indian situation. Vaccine. 2014; 32(28):3488–3494. https://doi.org/10.1016/j.vaccine.2014.04.053 PMID: 24795229

160. Kumar B, Manjunathachar HV, Nagar G, Ravikumar G, de la Fuente J, Saravanan BC, et al. Functional characterization of candidate antigens of *Hyalomma anatolicum* and evaluation of its cross-protective efficacy against *Rhipicephalus microplus*. Vaccine. 2017; 35(42):5682–5692.

161. Manjunathachar HV, Kumar B, Saravanan BC, Choudhary S, Mohanty AK, Nagar G, et al. Identification and characterization of vaccine candidates against *Hyalomma anatolicum*-Vector of Crimean-Congo haemorrhagic fever virus. Transbound Emerg Dis. 2019; 66(1):422–434. https://doi.org/10.1111/tbed.13038 PMID: 30300470

162. El Hakim AE, Shahein YE, Abdel-Shafy S, Abouelella AM, Hamed RR. Evaluation of glycoproteins purified from adult and larval camel ticks (Hyalomma dromedarii) as a candidate vaccine. J Vet Sci. 2011; 12(3):243–249. https://doi.org/10.4142/jvs.2011.12.3.243 PMID: 21897098

163. Ndawula C Jr, Tabor AE. Cocktail Anti-Tick Vaccines: The Unforeseen Constraints and Approaches toward Enhanced Efficacies. Vaccines (Basel). 2020; 8(3). https://doi.org/10.3390/vaccines8030457 PMID: 32824962

164. Shrivastava N, Verma A, Dash PK. Identification of functional epitopes of structural proteins and in-silico designing of dual acting multiepitope anti-tick vaccine against emerging Crimean-Congo hemorrhagic fever virus. Eur J Pharm Sci. 2020; 151:105396. https://doi.org/10.1016/j.ejps.2020.105396 PMID: 32479862

165. Cerny J, Lynn G, Hrnkova J, Golovchenko M, Rudenko N, Grubhoffer L. Management Options for *Ixodes ricinus*-Associated Pathogens: A Review of Prevention Strategies. Int J Environ Res Public Health. 2020; 17(6). https://doi.org/10.3390/ijerph17061830 PMID: 32178257

166. Burthe SJ, Schafer SM, Asaaga FA, Balakrishnan N, Chanda MM, Darshan N, et al. Reviewing the ecological evidence base for management of emerging tropical zoonoses: Kyasanur Forest Disease in India as a case study. PLoS Negl Trop Dis. 2021; 15(4):e0009243. https://doi.org/10.1371/journal.pntd.0009243 PMID: 33793560

167. Eisen L, Dolan MC. Evidence for Personal Protective Measures to Reduce Human Contact With Blacklegged Ticks and for Environmentally Based Control Methods to Suppress Host-Seeking Blacklegged Ticks and Reduce Infection with Lyme Disease Spirochetes in Tick Vectors and Rodent Reservoirs. J Med Entomol. 2016; 53(5):1063–1092. https://doi.org/10.1093/jme/tjw103 PMID: 27439616

168. Hubálek Z, Halouzka J, Juricova Z, Sikutova S, Rudolf I. Effect of forest clearing on the abundance of *Ixodes ricinus* ticks and the prevalence of *Borrelia burgdorferi* s.l. Med Vet Entomol. 2006; 20(2):166–172.

169. Clymer BC, Howell DE, Hair JA. Environmental alteration in recreational areas by mechanical and chemical treatment as a mMeans of Lone Star tick control. J Econ Entomol. 1970; 2:504–509.

170. Gleim ER, Conner LM, Berghaus RD, Levin ML, Zemtsova GE, Yabsley MJ. The phenology of ticks and the effects of long-term prescribed burning on tick population dynamics in southwestern Georgia and northwestern Florida. PLoS ONE. 2014; 9(11):e112174. https://doi.org/10.1371/journal.pone.0112174 PMID: 25375797

171. Stafford KI. Impact of controlled burns on the abundance of *Ixodes scapularis* (Acari: Ixodidae). J Med Entomol. 1998; 35:510–513. https://doi.org/10.1093/jmedent/35.4.510 PMID: 9701937

172. Allan BF. Influence of prescribed burns on the abundance of *Amblyomma americanum* (Acari: Ixodidae) in the Missouri Ozarks. J Med Entomol. 2009; 46(5):1030–1036. https://doi.org/10.1603/033.046.0509 PMID: 19769033

173. Minshull NI, Norval J. Factors influencing the spatial distribution of *Rhipicephalus appendiculatus* in Kyle Recreational Park, Zimbabwe. S Afr J Wildl Res. 1982; 12:118–123.

174. Civitello DJ, Flory SL, Clay K. Exotic grass invasion reduces survival of *Amblyomma americanum* and *Dermacentor variabilis* ticks (Acari: Ixodidae). J Med Entomol. 2008; 45(5):867–872. https://doi.org/10.1603/0022-2585(2008)45[867:egirso]2.0.co;2 PMID: 18826028

175. Norval RAI, Tebele N, Short NJ, Clatworthy JN. Laboratory study on the control of economically important tick species with legumes of the genus *Stylosanthes*. Zimb Vet J. 1983; 14(1):26–29.

176. Gilbert L, Maffey GL, Ramsay SL, Hester AJ. The effect of deer management on the abundance of *Ixodes ricinus* in Scotland. Ecol Appl. 2012; 22:658–667. https://doi.org/10.1890/11-0458.1 PMID: 22611862

177. Rand PW, Lubelczyk C, Holman MS, Lacombe EH, Smith RP. Abundance of *Ixodes scapularis* (Acari: Ixodidae) after the complete removal of deer from an isolated offshore island, endemic for Lyme disease. J Med Entomol. 2004; 4:779–784. https://doi.org/10.1603/0022-2585-41.4.779 PMID: 15311475

178. Jordan RA, Schulze TL, Jahn MB. Effects of reduced deer density on the abundance of *Ixodes scapularis* (Acari: *Ixodidae*) and Lyme disease incidence in a northern New Jersey endemic area. J Med Entomol. 2007; 44(5):752–757. https://doi.org/10.1603/0022-2585(2007)44[752:eorddo]2.0.co;2 PMID: 17915504

179. Del Fabbro S. Fencing and mowing as effective methods for reducing tick abundance on very small, infested plots. Ticks Tick Borne Dis. 2015; 6(2):167–172. https://doi.org/10.1016/j.ttbdis.2014.11.009 PMID: 25499616

180. Ginsberg HS, Butler M, Zhioua E. Effect of deer exclusion by fencing on abundance of *Amblyomma americanum* (Acari: Ixodidae) on Fire Island, New York, USA. J Vector Ecol. 2002; 27(2):215–221. PMID: 12546457

181. Valcarcel F, Gonzalez J, Tercero-Jaime JM, Olmeda AS. The effect of excluding ungulates on the abundance of *Ixodid* ticks on wild rabbit (*Oryctolagus cuniculus*). Exp Appl Acarol. 2017; 72(4):439–447. https://doi.org/10.1007/s10493-017-0166-2 PMID: 28840404

182. Hoch T, Breton E, Vatansever Z. Dynamic modeling of Crimean Congo Hemorrhagic Fever Virus (CCHFV) spread to test control strategies. J Med Entomol. 2018; 55(5):1124–1132. https://doi.org/10.1093/jme/tjy035 PMID: 29618023

183. Ostfeld RS, Keesing F. Effects of host diversity on infectious disease. Annu Rev Ecol Evol Syst. 2012; 43(1):157–182.

184. Levi T, Kilpatrick AM, Mangel M, Wilmers CC. Deer, predators, and the emergence of Lyme disease. Proc Natl Acad Sci U S A. 2012; 109(27):10942–10947. https://doi.org/10.1073/pnas.1204536109 PMID: 22711825

185. Hofmeester TR, Jansen PA, Wijnen HJ, Coipan EC, Fonville M, Prins HHT, et al. Cascading effects of predator activity on tick-borne disease risk. Proc R Soc Lond B Biol Sci. 1859; 2017(284):20170453.

186. Wilkinson P. The spelling of pasture in cattle tick control. Crop Pasture Sci. 1957; 8(4):414–423.

187. Barré N. Mesures agronomiques permettant une diminution des populations de la tiques *Amblyomma variegatum*. Rev Elev Med Vet Pays Trop. 1998; 41(4).

188. Bianchi MW, Barré N. Factors affecting the detachment rythm of engorged *Boophlilus microplus* female ticks (Acari: Ixodidae) from Charolais steers in New Caledonia. Vet Parsitol. 2003; 112:325–336.

189. Stachurski F, Adakal H. Exploiting the heterogeneous drop-off rhythm of *Amblyomma variegatum* nymphs to reduce pasture infestation by adult ticks. Parasitology. 2010; 137(7):1129–1137.

190. White J, Heylen DJ, Matthysen E. Adaptive timing of detachment in a tick parasitizing hole-nesting birds. Parasitology. 2012; 139(2):264–270. https://doi.org/10.1017/S0031182011001806 PMID: 22067275

191. Masika PJ, Sonandi A, van Averbeke W. Tick control by small-scale cattle farmers in the central Eastern Cape Province, South Africa. J S Afr Vet Assoc. 1997; 68(2):45–48. https://doi.org/10.4102/jsava.v68i2.868 PMID: 9291072

192. Bonnet SI, Pollet T. Update on the intricate tango between tick microbiomes and tick-borne pathogens. Parasite Immunol. 2020:e12813. https://doi.org/10.1111/pim.12813 PMID: 33314216

193. van Tol S, Dimopoulos GI. Influences of the Mosquito Microbiota on Vector Competence. Adv Insect Physiol. 2016; 51:243–291.

194. Mateos-Hernandez L, Obregon D, Maye J, Borneres J, Versille N, de la Fuente J, et al. Anti-Tick Microbiota Vaccine Impacts *Ixodes ricinus* Performance during Feeding. Vaccines (Basel). 2020; 8(4).

195. Abraham NM, Liu L, Jutras BL, Yadav AK, Narasimhan S, Gopalakrishnan V, et al. Pathogen-mediated manipulation of arthropod microbiota to promote infection. Proc Natl Acad Sci U S A. 2017; 114 (5):E781–E790. https://doi.org/10.1073/pnas.1613422114 PMID: 28096373

196. Azagi T, Klement E, Perlman G, Lustig Y, Mumcuoglu KY, Apanaskevich DA, et al. *Francisella*-Like Endosymbionts and *Rickettsia* Species in Local and Imported *Hyalomma* Ticks. Appl Environ Microbiol. 2017; 83(18).

197. Elbir H, Almathen F, Elnahas A. Low genetic diversity among *Francisella*-like endosymbionts within different genotypes of *Hyalomma dromedarii* ticks infesting camels in Saudi Arabia. Vet World. 2020; 13(7):1462–1472. https://doi.org/10.14202/vetworld.2020.1462-1472 PMID: 32848325

198. Ivanov IN, Mitkova N, Reye AL, Hubschen JM, Vatcheva-Dobrevska RS, Dobreva EG, et al. Detection of new *Francisella*-like tick endosymbionts in *Hyalomma* spp. and *Rhipicephalus* spp. (Acari: Ixodidae) from Bulgaria. Appl Environ Microbiol. 2011; 77(15):5562–5565. https://doi.org/10.1128/AEM.02934-10 PMID: 21705542

199. Szigeti A, Kreizinger Z, Hornok S, Abichu G, Gyuranecz M. Detection of *Francisella*-like endosymbiont in *Hyalomma rufipes* from Ethiopia. Ticks Tick Borne Dis. 2014; 5(6):818–820. https://doi.org/10.1016/j.ttbdis.2014.06.002 PMID: 25108781

200. Adegoke A, Kumar D, Bobo C, Rashid MI, Durrani AZ, Sajid MS, et al. Tick-Borne Pathogens Shape the Native Microbiome Within Tick Vectors. Microorganisms. 2020; 8(9). https://doi.org/10.3390/microorganisms8091299 PMID: 32854447

201. Gowrishankar S, Ravi Latha B, Sreekumar C, Leela V. Solar tick trap with a pheromone lure—A stand-in approach for off-host control of *Rhipicephalus sanguineus* sensu lato ticks. Ticks Tick Borne Dis. 2021; 12(3):101656. https://doi.org/10.1016/j.ttbdis.2021.101656 PMID: 33529987

202. Almazan C, Simo L, Fourniol L, Rakotobe S, Borneres J, Cote M, et al. Multiple Antigenic Peptide-Based Vaccines Targeting *Ixodes ricinus* Neuropeptides Induce a Specific Antibody Response but Do Not Impact Tick Infestation. Pathogens. 2020; 9(11).

203. Le Mauff A, Chouikh H, Cartereau A, Charvet CL, Neveu C, Rispe C, et al. Nicotinic acetylcholine receptors in the synganglion of the tick *Ixodes ricinus*: Functional characterization using membrane microtransplantation. Int J Parasitol Drugs Drug Resist. 2020; 14:144–151.