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EDITORIAL

New challenges posed by ticks and tick-borne diseases

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Ticks are ectoparasites of terrestrial vertebrates and amphibians, causing blood loss and damage to the skin of their hosts. Even more importantly, ticks are vectors of a wide range of pathogenic microorganisms (viruses, bacteria, protozoa) of public health and veterinary relevance worldwide (Sonenshine and Roe 2014). Due to global changes (climatic, environmental and socioeconomic) the number of tick-borne disease cases in humans and animals is increasing, ticks and the pathogens they carry expand to new geographic areas and new tick-borne pathogens and diseases are being identified (Madison-Antenucci et al. 2020; Rochlin and Toledo 2020; Gilbert 2021; Nuttall 2022a). There are still gaps in the knowledge of tick ecology, tick-host-pathogen interactions, circulation of tick-borne pathogens in natural foci and epidemiology of the diseases. Ticks, in addition to their vector role, can cause various kinds of toxicoses and trigger red-meat allergy that are intriguing biological phenomena (Cabezas-Cruz et al. 2019; Apari and Földvári 2021, 2022). They are highly interesting organisms also due to their complex life cycles and sophisticated feeding strategies (Sonenshine and Roe 2014). The fact that most tick species, in contrast to blood-feeding insects, remain attached to their hosts and feed for prolonged periods of time, opened the field for studies on physiology of tick feeding, tick-host-pathogen interactions on cellular and molecular level, interactions between microorganisms in ticks in case of coinfections, pharmacology of molecules contained in saliva that are injected by feeding ticks into the skin attachment site to counteract host defence reactions, as well as to investigations of the processes on the tick-host interface during transmission of pathogens (e.g. Šimo et al. 2017; Neelakanta and Sultana 2022). As ticks have great impact on human and veterinary medicine, their control is inevitable. However, application of chemical acaricides is limited in time as ticks develop resistance and, even more importantly, acaricides cause pollution of the environment. For these reasons, new tick control strategies are explored. One of such strategies is the development of acaricides based on natural products derived from plants (Quadros et al. 2020). The development of anti-tick vaccines is another promising strategy, which is based on immunization with antigens derived from ticks that induce immunity to tick infestation (Willadsen 2004). However, the main goal is to find the antigen (or cocktail of several antigens) which, in addition to reducing tick infestation, would prevent transmission of pathogens (i.e. transmission blocking vaccines). During the last two decades, a plethora of molecules derived from saliva, gut or other tick organs have been identified and tested as vaccine candidates. However, the scientific community is still searching for the "ideal" anti-tick and transmission blocking vaccine (van Oosterwijk 2021; van Oosterwijk and Wikel 2021).

This special issue of the journal *Biologia* is devoted to new challenges posed by ticks and tick-borne diseases and contains one invited review, four reviews, one opinion, and ten original papers. The articles are dealing with different aspects of tick biology and ecology, tick-host-pathogen interactions, epidemiology of tick-borne diseases, and progress in the search for new control methods to combat ticks and prevent transmission of tick-borne pathogens. The papers included in this special issue were written by authors from 11 countries (Brazil, Canada, Czech Republic, China, Cuba, France, Pakistan, Poland, Slovakia, Ukraine, United Kingdom).

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Pat Nuttall discusses in her review article current knowledge and future scenarios on the impacts of climate change on ticks and tick-borne infections (Nuttall 2022b). This review illustrates that there is lack of direct evidence that climate change alone affects the abundance and spatial distribution of ticks and the occurrence and prevalence of tick-borne diseases. There are, however, a few examples such as the expansion of *Ixodes scapularis* and Lyme borreliosis in northwestern USA and their establishment in Canada related to the 2–3 °C increase in land surface temperature, or the expansion of *Ixodes ricinus* and associated Lyme borreliosis and tick-borne encephalitis to northern Europe and to higher altitudes. Moreover, the occurrence of some exotic species, such as *Rhipicephalus sanguineus* or *Hyalomma marginatum* was recorded in more northern latitudes in Europe than a few decades ago. To predict future scenarios of the spread of ticks and diseases they transmit, in addition to climate, other factors such as tick physiology and phenology, land use change, density and diversity of vertebrate host populations, and livestock and wildlife management should be considered. However, in regions where tick-borne infections of livestock directly affect humans, the One Health approach should be applied. Thus, control of ticks and management of tick-borne diseases in the era of global changes is not straightforward and depends, in addition to climate change, on many other factors.

As already stated, during the latest decades the geographic distribution of many vectors and pathogens has changed. *Dermacentor reticulatus* is one of these species whose increase in abundance and expansion to new areas has been observed in Europe since the 1990s. Karbowiak (2022) discusses possible causes for the spread of *D. reticulatus* to new geographical areas and urban agglomerations. These may include changes in the average summer and winter temperature in Europe, changes in the use of agricultural and forest areas, and changes in the distribution and abundance of the main hosts of adult ticks, such as elk *Alces alces*, red deer *Cervus elaphus*, raccoon dog *Nyctereutes procyonoides* and the red fox *Vulpes vulpes*.

Didyk et al. (2022) document the first occurrence of *R. sanguineus* s.l. populations in south-western Slovakia that were found indoors, in two family flats. Genetically, the ticks were found to belong to the lineage from the Mediterranean region. Future cases of introduction through dogs traveling with their owners to endemic regions, or even the establishment of *R. sanguineus* populations in Slovakia are predictable. Careful monitoring of dogs imported or returning from abroad for this exotic tick species is necessary to avoid infestations of domestic dogs and the introduction and spread of pathogens transmitted by *R. sanguineus*.

Tick-borne infections represent a major threat to humans and livestock, but there are only a few effective vaccines for prevention. In this light, Hromníková et al. (2022) provide an overview of the current knowledge on existing vaccines against tick-borne infections with the focus on humans and livestock. Moreover, the authors present novel strategies of protection against ticks and tick-borne diseases that are focused on the feeding stage of ticks during which pathogens are transmitted. Food intake, saliva production, reproduction, development and other physiological functions in ticks are controlled by neuropeptides and peptide hormones which may also be involved in pathogen transmission. Thus, vaccines that subvert the function of neuropeptides and hormones in the feeding ticks could represent another, modern strategy to combat ticks and the transmission of pathogens.

Ticks coexist and interact, in addition to pathogenic microorganisms, with symbionts, and commensal bacteria. These together form an ecological unit, the tick holobiont, which also undergoes natural selection. Thus, antibiotic treatment may disturb the tick-microbiota homeostasis, decrease tick fitness and affect tick-pathogen interactions. Wu-Chuang et al. (2022) hypothesize that targeting the key members of the bacterial community of the tick microbiome by host antibodies could cause microbial dysbiosis with consequences for tick physiology and vector competence. Anti-tick microbiota vaccines have been recently introduced to target the microbiota of the vector by immunizing vertebrate hosts against key members of the tick microbiota bacterial proteins. This tool can also be used to target tick endosymbionts. A decrease in abundance of selected bacteria or endosymbionts may then change the structure of the tick microbiome in a predictable manner. Anti-tick microbiota vaccines could be used to manipulate the tick microbiome against the ticks as well as transmitted pathogens. The authors of this opinion paper explore the possibilities of the described methodology to control ticks and tick-borne diseases.

Ticks are vectors of causative agents of a number of diseases in livestock, such as babesiosis, theileriosis, Crimean-Congo haemorrhagic fever etc., and cause huge economic losses and zoonotic risks also for the human population in Pakistan. Hussain et al. (2022) compiled data on ticks of Pakistan and reviewed literature on this topic published between 1947 and early 2021. However, the authors focused only on studies that included ticks identified on cattle, buffaloes, sheep, and goats. A total of 30 tick species of seven genera have been identified from cattle and buffaloes, 40 species of seven genera have been found on sheep and goats. The updated list of the tick fauna and of tick-host relationships compiled in the present review will help to predict future economic risks and potential animal health losses associated with these parasites in Pakistan. In addition, the results may help in proposing tick control and prevention strategies under the One Health approach.

Slovakia is a country with a long tradition in the research of ticks and tick-borne diseases and has achieved results of high relevance. Stanko et al. (2022) in the review on ticks and their epidemiological role in Slovakia give a comprehensive historical overview of research in this particular field with important milestones and recent findings, and outline challenges and future directions in the investigation of ticks as ectoparasites and vectors of zoonotic agents. Due to climate change and urbanization, there is a risk of the introduction and spread of known tick-borne pathogens from endemic regions, or the emergence of new pathogens with unknown ecology and etiology. The development of modern molecular tools has led to the discovery and identification of emerging or new tick-borne microorganisms and symbionts with unknown zoonotic potential. However, proper diagnostic tools to identify neglected or unknown diseases are lacking and as a consequence, many cases of tick-borne diseases remain undiagnosed or misdiagnosed. Coinfections of pathogens in ticks require clinicians to consider mixed symptoms in their diagnosis. Thus, the most important future tasks for Slovak tick researchers and epidemiologists are (i) monitoring of changes in the abundance and diversity of ticks and vertebrate hosts, (ii) screening their infection with pathogenic microorganisms, (iii) investigating of genetic diversity of the detected microorganisms, (iv) proper diagnosis of the related diseases, and (v) introducing preventive measures and treatments.

The Slovak Karst in eastern Slovakia is a unique area in Central Europe, with the sympatric occurrence of seven tick species (*Ixodes ricinus, I. trianguliceps, I. frontalis, Dermacentor marginatus, D. reticulatus, Haemaphysalis concinna, H. inermis*) and great diversity of vertebrate hosts (cattle, different wildlife species) (Černý 1972; Nosek 1972; Bona and Stanko 2013; Heglasová et al. 2020). The presence of another species, *Haemaphysalis punctata*, which dominated there in the previous century, has not been confirmed recently. Due to its uniqueness, the Slovak Karst where the host range of the tick species overlaps, represents an ideal model area for investigation of the circulation of a number of tick-borne pathogens and the pathogen flow between individual tick species. Results of two recent studies that were carried out in Slovak Karst were summarised in papers by Ouarti et al. (2022) and Bona et al. (2022). Ouarti et al. (2022) analysed the bacterial community, particularly *Rickettsia* spp., in questing *D. reticulatus* and *H. inermis.* By molecular tools the authors detected the occurrence of *Rickettsia* spp., and by sequencing of selected samples they confirmed the presence of *Rickettsia raoultii* in both tick species. These results suggest that *D. reticulatus* and *H. inermis* may be involved in the transmission cycle of *R. raoultii*. However, to prove this hypothesis, transmission models in the laboratory will be needed. Bona et al. (2022) investigated the influence of climatic conditions such as temperature, relative humidity, and saturation deficit for each tick species present in the Slovak Karst. *Ixodes ricinus* was the most abundant species, followed by *H. inermis*, *D. marginatus* and *D. reticulatus*. In addition, questing ticks were examined for the presence of selected zoonotic bacteria and piroplasmids. *Ixodes ricinus* was found to harbour the widest spectrum of pathogens. Spirochetes from the *Borrelia burgdorferi* s.l. complex prevailed (*Borrelia garinii* and *B. afzelii* dominated), followed by *Babesia* spp. (presence of *Babesia microti* and *B. venatorum* was confirmed), and *Anaplasma phagocytophilum*. Interestingly, borreliae were detected in questing *D. reticulatus* and *H. inermis,* which raises the question if these tick species are also involved in transmission of borreliae.

In Slovakia, Lyme borreliosis (LB), tick-borne encephalitis, rickettsioses and Q-fever are communicable diseases. On the other hand, human granulocytic anaplasmosis (HGA), babesiosis or others (e.g. neoehrlichiosis) are still neglected, with very low numbers or no confirmed cases, although presence of the causative agents have been detected in ticks as well as in vertebrate hosts. Based on serological and molecular analyses of human sera and blood of patients obtained during 2011–2020, results of laboratory testing, history of tick-bites and description of symptoms of the diseases, Špitalská et al. (2022) described seven cases of diseases related to rickettsiae (*Rickettsia helvetica, R. raoultii*, *Rickettsia* sp.), Q-fever and, for the first time in Slovakia, HGA with the presence of *A. phagocytophilum* DNA in a human patient's blood for 47 days. Zubriková et al. (2022) report the molecular evidence of a *Rickettsia*-like infection in a human patient from Slovakia, who reported no history of tick-bite, but bites by an unknown flying insect. The data obtained by the cited authors suggest that an effective surveillance of rickettsioses, *Rickettsia*-like infections as well as of other emerging tick-borne diseases is required for their prevention and is an ongoing task for public health authorities in Slovakia.

Coxiella burnetii is another zoonotic pathogen that causes Q-fever in humans and animals. Although relatively well studied, there are still gaps in the knowledge of the epidemiology of the disease. A possible role of horses as sources of *C. burnetii* for other animals and humans has been indicated (Marenzoni et al. 2013). Drážovská et al. (2022) initiated a serosurvey of the pathogen in horse sera in Slovakia and for the first time, they detected specific antibodies against *C. burnetii* in a few horses in central and eastern Slovakia. Their data can be the basis for further research of the role of horses in the epidemiology of Q-fever.

Lyme borreliosis (LB) is the most prevalent tick-borne disease in Europe. The disease is caused by spirochetes of the *B. burgdorferi* s.l. complex and *I. ricinus* is its principal vector. The EU case definition of Lyme neuroborreliosis was published in 2018, and neuroborreliosis has become reportable to the European Surveillance System (European Commission 2018). Orlíková et al. (2022) describe the LB surveillance and reporting system in the Czech Republic and present epidemiological characteristics of LB for 2018 and 2019. They also identify gaps and limitations of the existing national LB surveillance system, especially concerning reporting of neuroborreliosis according to the EU case definition, and requirements to fully implement the EU neuroborreliosis surveillance system in the Czech Republic.

Small mammals such as rodents and insectivores are frequently infested by different groups of ectoparasites, including ticks. Moreover, small mammals are important reservoirs of a number of zoonotic diseases. Karbowiak et al. (2022) analyse the associations between ectoparasitic arthropods and root voles (*Microtus oeconomus*) in north-eastern Poland. Among ticks, *Ixodes apronophorus* was recorded on *M. oeconomus* in Poland for the first time. The authors observed the presence of *D. reticulatus* larvae and nymphs only in July and August – the intensity of infestation of the root voles by this tick species was about two times higher in July than in August, when it was partly replaced by *I. ricinus* and fleas. Larvae of *D. reticulatus* prevailed in July and nymphs in August. These findings correspond to the seasonal changes of tick infestation of other rodent species.

Tick control is among urgent tasks in the management of tick infestations of livestock worldwide. As ticks become resistant to acaricides, introduction of more effective and environment-friendly measures of tick control are urgently needed. Application of extracts of plants is among promising alternatives to acaricides. Sousa da Costa et al. (2022) demonstrated the acaricide activity of *Ximenia americana* (Olacaceae) stem bark hydroethanolic extract and its ability to support the action of cypermethrin on mortality and oviposition of *Rhipicephalus (Boophilus) microplus*, an economically important bovine ectoparasite. This study opens the way to further studies on isolation and identification of the active compounds in *X. americana* and their possible use in tick control.

It is well known that ticks are not live syringes taking blood from and injecting pathogenic microorganisms into their hosts, but they are efficient „pharmacologists", modulating diverse host defence reactions (Ribeiro 1995). In connection with their unique feeding strategy, ticks possess a wide spectrum of salivary molecules that ensure their prolonged attachment to the host skin through counteracting host defences and may also serve as candidates for development of pharmaceuticals (Štibrániová et al. 2019). In spite of increasing knowledge of the composition of tick saliva and function of its molecules, there is still more „unknown "than „known "in this field. Bartikova et al. (2022) compared the effect of salivary gland extracts (SGE) of different tick species on the cytotoxic activity of murine Natural killer (NK) cells *in vivo*. NK cells belong to the main cellular components of the vertebrate innate immunity and recognize and eliminate pathogen-infected and tumour cells. Suppression of cytotoxic activity of human NK cells *in vitro* by SGE of adult *D. reticulatus* ticks has already been demonstrated previously (Kubes et al. 1994). Bartikova et al. (2022) demonstrated that SGE derived from partially fed adults of *D. reticulatus, Amblyomma variegatum* and *H. concina* inhibited cytotoxic activity of mouse NK cells. Interestingly, SGE of *I. ricinus*, *H. inermis*, *Rhipicephalus appendiculatus* and *R. pulchellus* did not show this effect. Based on preliminary results, the authors assume that the active molecule(s) is (are) basic protein(s) with a molecular weight of ca. 30 kDa, but further studies are needed to identify and characterise the molecule(s).

The papers in this special issue highlight different areas where further research is needed, but they are not even close covering all unexplored aspects of tick biology and ecoepidemiology of tick-borne diseases. We hope that these articles will inspire scientists to provide us further significant findings.

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