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Review

Managing mosquitoes and ticks in a rapidly changing world – Facts and trends

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A B S T R A C T

Vector-borne diseases transmitted by mosquitoes and ticks are on the rise. The effective and sustainable control of these arthropod vectors is a puzzling challenge for public health worldwide. In the present review, I attempted to provide a concise and updated overview of the current mosquito and tick research scenario. The wide array of control tools recently developed has been considered, with special reference to those approved by the World Health Organization Vector Control Advisory Group (WHO VCAG), as well as novel ones with an extremely promising potential to be exploited in vector control programs. Concerning mosquitoes, a major focus has been given on genetically modified vectors, eave tubes, attractive toxic sugar baits (ATSB) and biocontrol agents. Regarding ticks, the recent development of highly effective repellents and acaricides (including nanoformulated ones) as well as behavior-based control tools, has been highlighted. In the second part of the review, key research questions about biology and control of mosquitoes and ticks have been critically formulated. A timely research agenda outlining hot issues to be addressed in mosquito and tick research is provided. Overall, it is expected that the present review will contribute to boost research and applications on successful mosquito and tick control strategies, along with an improved knowledge of their biology and ecology.

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Contents

1. Introduction 921
2. Control of mosquitoes and ticks – Towards an eco-friendly scenario? 923
3. Major research questions on mosquitoes 923
4. Major research questions on ticks. 924
5. Conclusive remarks and future challenges 925
Acknowledgements 926
Conflict of interest 926
References 926

1. Introduction

The world is now subjected to rapid environmental changes, along with the fast, unintended spread of invasive pests and vectors through commercial and migration routes (Keirans and Durden, 2001; Schaffner et al., 2013; Medlock et al., 2015; Akiner et al., 2016; Kelehear et al., 2017). In this scenario, the effective and sustainable control of arthropod vectors is a puzzling challenge for public health worldwide (Benelli and Duggan, 2018 De Fuentes-Vicente et al., 2018; Fernandes et al., 2018a), with special reference to local communities in developing countries, which experience poor access to adequate diagnostics, prevention and treatment of infectious diseases (Bergquist et al., 2017; Molyneux et al., 2017).

Vector-borne diseases transmitted by mosquitoes and ticks are on the rise (Rosenberg et al., 2018). Despite decades of extensive

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research efforts, Culicidae still play a crucial role among vectors of medical and veterinary importance (Benelli, 2015; Saifi et al., 2016). The malaria burden is widely recognized for its importance in tropical and subtropical countries. In this context, with about forty *Anopheles* competent vectors (Fig. 1) (CDC, 2015), it leads to 6.8 million deaths averted globally since 2001, worsened by the fact that the recently released malaria vaccine only showed transient protection (Gosling and von Seidlein, 2016). In addition to this, malaria cases in European countries have been also registered, including fatal ones (Benelli et al., 2018a).

Furthermore, dengue virus poses at risk 3900 million people in 128 countries (Bhatt et al., 2013; Al-Shami et al., 2014), and lymphatic filariasis is still ranked among the most important neglected tropical diseases (Jambulingam et al., 2016). At the same time – Zika virus outbreaks in the Americas and the Pacific are attracting high public health attention (Petersen et al., 2016; Yakob and Walker, 2016; Benelli and Romano, 2017), due to the arboviral connection with fetal microcephaly and neurological complications, particularly the Guillain–Barré syndrome (Oehler et al., 2014; Benelli and Mehlhorn, 2016). The spread of arboviral diseases is continuous and hard to deal with, as very recently showed by a case of Keystone virus isolated from a Florida teenager with rash and fever (Lednicky et al., 2018).

Ticks are fascinating organisms, which can transmit an extremely high number of infectious agents to humans, livestock, pets, and wildlife (Fig. 2) (Guglielmone et al., 2014; Pantchev et al., 2015; Diuk-Wasser et al., 2016; Banumathi et al., 2017; Boka et al., 2017). Besides the rise in the number of cases of Lyme

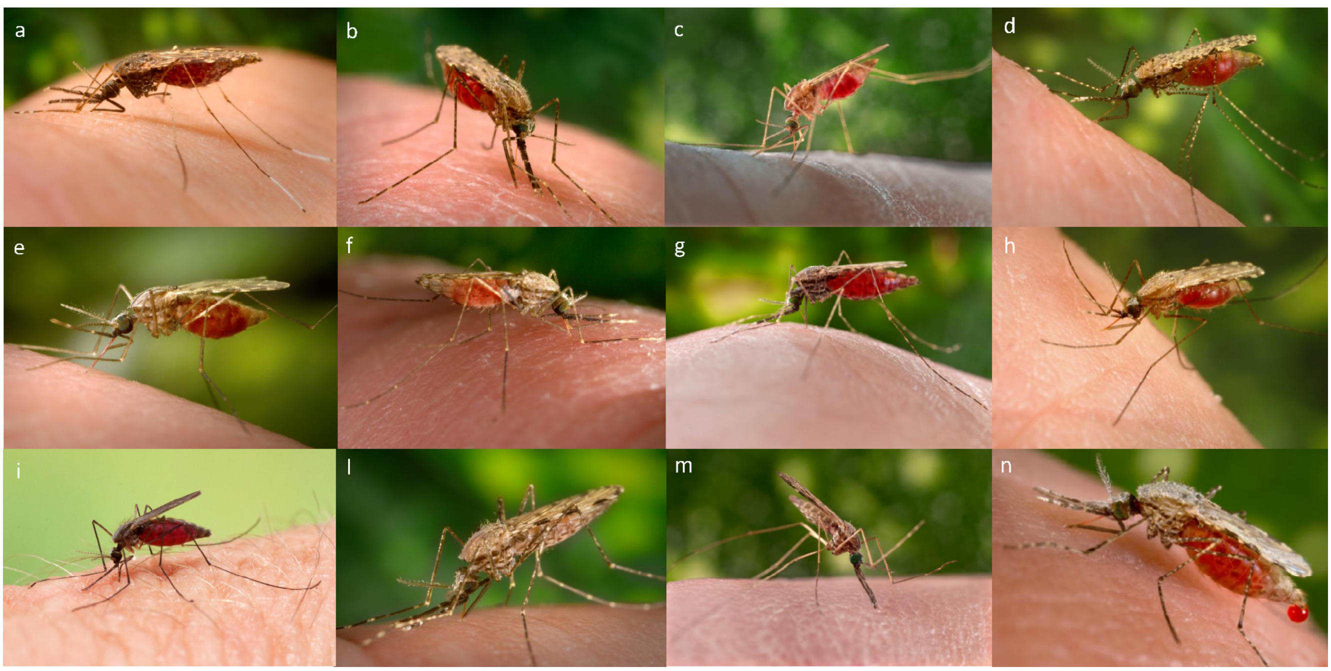

Fig. 1. Several *Anopheles* species acting as malaria vectors: (a) *Anopheles albimanus*, (b) *Anopheles arabiensis* (c) *Anopheles atroparvus*, (d) *Anopheles farauti*, (e) *Anopheles funestus*, (f) *Anopheles gambiae*, (g) *Anopheles merus*, (h) *Anopheles minimus*, (i) *Anopheles plumbeus*, (l) *Anopheles quadriannulatus*, (m) *Anopheles sinensis*, and (n) *Anopheles stephensi* (photo credit: *A. plumbeus*: ECDC; *A. stephensi*: Dr. W. Collins; others: Dr. J. Gathany, CDC-PHIL).

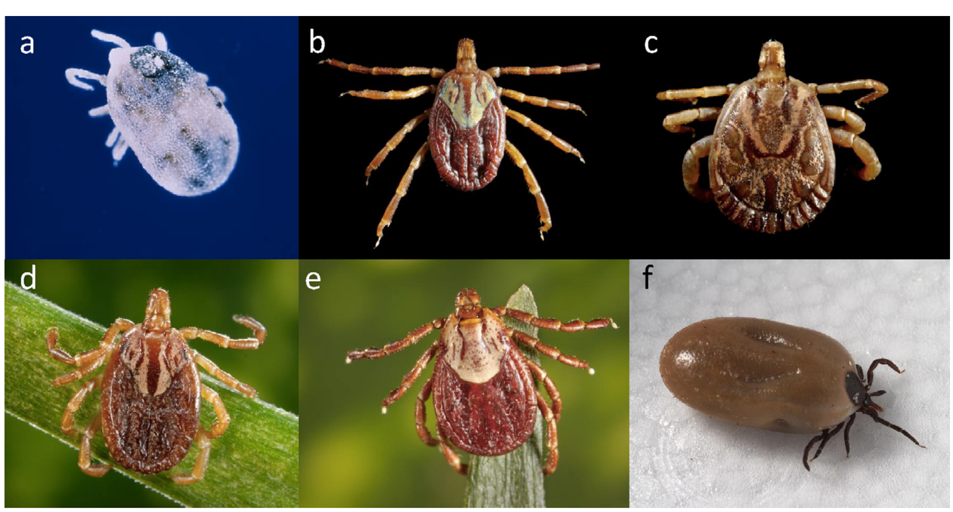

Fig. 2. Ticks act as major vectors of medical and veterinary importance. Among soft ticks, is worthy of mention (a) *Ornithodoros hermsi*, vectoring a bacterial disease called tick-borne relapsing fever. Hard ticks play a major role as pathogen vectors, including – among others – (b) the Gulf Coast tick, *Amblyomma maculatum* (female here), (c) the cayenne tick, *Amblyomma cajennense* (male here), (d) *Amblyomma triste* (female here), (e) the Rocky Mountain wood tick, *Dermacentor andersoni* (female here), and (f) the blacklegged deer tick, *Ixodes scapularis* (engorged female here) (photo credit: courtesy of Dr. J. Gathany, CDC-PHIL, except for *I. scapularis*, Dr. G. Alpert).

disease, caused by genospecies of the *Borrelia burgdorferi* s.l. complex (CDC, 2017), important tick-borne diseases also include anaplasmosis, ehrlichiosis, Rocky Mountain spotted fever, Powassan virus, and babesiosis (Lani et al., 2014; Buckingham, 2015; Ostfeld and Brunner, 2015; Inci et al., 2016; Solano-Gallego et al., 2016; de la Fuente et al., 2017).

In the present work, I attempted to provide a concise and update overview of the current mosquito and tick research scenario, reinforcing basic opinions of vector experts globally (Fernandes et al., 2018a). The wide array of control tools recently developed has been considered, with special reference to those approved by the WHO Vector Control Advisory Group (WHO VCAG), as well as novel ones with an extremely promising potential to be exploited in Integrated Vector Management (IVM), which suggests making use of the full range of vector control tools available, avoiding "vertical" management structures relying only on one form of vector control (Beier et al., 2008; Benelli and Beier, 2017). In the second part of the article, major research questions about biology and control of mosquitoes and ticks have been critically formulated. Therefore, a research agenda outlining hot issues to be addressed in mosquito and tick research is provided.

2. Control of mosquitoes and ticks – Towards an eco-friendly scenario?

To effectively manage mosquito populations, a rather wide number of control routes have been attempted, including classic applications of chemical pesticides (Strode et al., 2014) as well as microbial ones (e.g., toxins from *Bacillus thuringiensis israelensis*) (Melo et al., 2016; Alkenani, 2017), wide employ of long-lasting insecticidal nets (LLINs) (Tiono et al., 2015; Hamainza et al., 2016; Tan et al., 2016) and indoor residual spraying (IRS) (West et al., 2014; Paredes-Esquivel et al., 2016), where the latter strongly contributed to malaria decline in sub-Saharan Africa (Benelli and Beier, 2017).

Besides, the development of eco-friendly formulations of novel insecticides (Isman, 2015, 2017), covering also nanostructured materials (Benelli, 2016a,b; Mishra et al., 2018), is rapidly gaining ground, along with the employ of attractive toxic sugar baits (ATSB) (Muller et al., 2010; Beier et al., 2012; Junnila et al., 2015; Qualls et al., 2015; Fiorenzano et al., 2017) and eave tubes (Knols et al., 2016; Sternberg et al., 2016). Travel medicine dedicated a major emphasis to mosquito repellents (Lupi et al., 2013), even this option is of applied significance mostly for tourists visiting regions with endemic vector-borne diseases, but cannot be a long-term solution for local communities living in these regions.

Besides, while biological control agents experienced a slow gradual decline in their applications, linked to the earlier massive detection of non-target effects due to several biocontrol agents (e.g., the mosquitofish, *Gambusia affinis* Baird and Girard) (Lacey et al., 2015; Benelli et al., 2016a), biotechnological tools are currently considered of high interest. The latter includes genetically modified mosquitoes, *Wolbachia*-based approaches [successfully used against important *Aedes* vectors, such as the yellow fever mosquito, *Aedes aegypti* (L.)], the sterile insect technique (SIT) (Zhang et al., 2015; Bourtzis et al., 2016; Joubert et al., 2016; Wilke et al., 2018).

However, according to the WHO VCAG, there is an urgent need to validate the most promising ones through epidemiological evidences (Wilke et al., 2018). Besides, despite the fast-growing research on the so-called "green" mosquito larvicides (e.g., plant extracts, essential oils, bacterial and fungal metabolites), it is worthy to note that they are not recommended for mosquito control in rural areas (Benelli and Beier, 2017).

A comparable scenario applies well to other important arthropod vectors. The effective and timely management of ticks is crucial to prevent tick-borne diseases (Willadsen, 2006; Drexler et al., 2014; Benelli, 2016c; Dantas-Torres and Otranto, 2016). Decades of intensive research on tick biology and control have strongly contributed to stress the relevance of:

- Timely and reliable molecular identification of tick vectors (Lv et al., 2014a,b; Zhang and Zhang, 2014) and their vertebrate hosts examining tick bloodmeals (Alcaide et al. 2009; Gariepy et al., 2012).
- Vaccine development (de la Fuente et al., 2007; de la Fuente and Contreras, 2015; Lew-Tabor and Valle, 2016).
- Genetic and genomic tools (Mapholi et al., 2014).
- Operations based on the IVM criteria lowering the interactions of ticks with livestock (Ghosh et al., 2006; Ghosh and Nagar, 2014).
- Tick chemoecology manipulation through pheromone-based tools (Sonenshine et al., 2002; Sonenshine, 2006).
- Plant-isolated repellents (Semmler et al., 2011; Benelli et al., 2016b), with a selected number of them now used in commercial formulations.
- Control programs based on the use of biocontrol agents (Samish and Rehacek, 1999; Gindin et al., 2002), including entomopathogenic fungi [e.g., *Metarhizium anisopliae* (Metchnikoff) Sorokin] (Webster et al., 2015).

However, despite the promising potential of the above-mentioned tools, the majority of tick control operations still rely to the use of synthetic acaricides (Dantas-Torres et al., 2012; Pfister and Armstrong, 2016; Brites-Neto et al., 2017). This leads to severe drawbacks (Estrada-Peña and Salman, 2013), with special reference to fast resistance development in targeted ticks (Abbas et al., 2014; Shyma et al., 2015; Vudriko et al., 2016), hazard risks for mammals (van Wieren et al., 2016), and livestock product contamination by acaricidal residues (Ghosh et al., 2006; Yavuz et al., 2017).

3. Major research questions on mosquitoes

Some of the most relevant research questions about mosquito biology and ecology focused on their impressive ability to adapt to new environments. This is the case, for instance, of the highly invasive species *Aedes (Stegomyia) albopictus* (Skuse), commonly known as the Asian tiger mosquito. This species has been able to spread and establish in northern Europe (Kraemer et al., 2015), due its huge ecological and physiological plasticity (Bonizzoni et al., 2013). In this framework, researchers can formulate various timely questions, including: which is the updated vectors status of mosquitoes widespread in Europe (Koch et al., 2016)? Besides, the same can apply to other areas worldwide. Also, a relevant research focus has been devoted to which mosquito species are endangering public health in Asian countries subjected to rapid urbanization (Li et al., 2014).

In addition to their well-established role as vectors of highly studied parasites and pathogens, we know relatively little about the potential role of mosquito vectors in spreading other, overlooked, infectious agents. As recently asked by several researchers, along with preliminary research evidences, a timely question is: what we really know about the potential carcinogenic action of some pathogens and parasites vectored by mosquitoes (Lehrer, 2010; Benelli et al., 2016c; Johansson and Ward, 2017; Ward and Benelli, 2017, 2018)?

Some basic facets of mosquito behavioral ecology and biology still needs to be elucidated. For example, it is surprising that – despite our rather wide knowledge on mosquito kairomones – we know little about the volatile compounds mediating swarming and mate recognition (Pitts et al., 2014; Vaníčková et al., 2017).

Furthermore, concerning mosquito control, crucial issues to deal with are: which are the main drawbacks arising from the use of chemical pesticides (Desneux et al., 2007; Chanda et al., 2016; Naqqash et al., 2016; Chang et al., 2017)? How outbreaks of mosquito-borne diseases can be prevented by proper modelling (Cosner et al., 2009; Ajelli, 2017)? Does the latter gives valuable information for vector control operations? Do herbal and microbial products represent a challenging solution to develop novel mosquito repellents and insecticides of commercial interest (Soonwera and Phasomkusolsil, 2015; Pavela and Benelli, 2016a, b)? Do long-lasting repellent- and insecticide-treated textiles have a promising potential in the fight against mosquitoes and other bloodsucking arthropods (Banks et al., 2014; Abdel-Ghaffar et al., 2015)? Do nanoparticles and nanoformulated pesticides have a real potential in the fight against mosquitoes (Benelli and Lukehart, 2017; Benelli, 2018a)? Which are their modes of action and fate in the aquatic environment (Benelli et al., 2018b,c)? Are they dangerous for human health (Foldbjerg et al., 2015; Benelli et al., 2017a)?

Last, but not least, it has been recently outlined that the management of mosquito vector populations can be achieved also considering the plant species complex characterizing the habitats where mosquitoes live. Indeed, adult mosquitoes can benefit from the large availability of some nectar-rich flowerings, and a significant number of them are invasive species that needs to be managed (Stone et al., 2018).

4. Major research questions on ticks

Notably, a number of research questions outlined for mosquito vectors apply well also on tick research (Figs. 3 and 4). A first good one would be: which is the real vector competence of many overlooked and poorly studied tick species (Estrada-Pen~a et al., 2017)? This question is of relevance especially in poor and marginalized areas of the world, where people, livestock and pets have limited access to advanced diagnostic tools. This applies both to hard and soft ticks (Manzano-Román et al., 2012).

Furthermore, despite a wide number of researches available on tick and tick-borne disease ecology (Pfäffle et al., 2013), important facets of their behavior still need to be elucidated. For example, the behavioral asymmetries of ticks during questing and related success, have been investigated only in a species, the castor bean tick, *Ixodes ricinus* (L.) (Benelli et al., 2018c), where population-level lateralized questing has been detected.

From a control perspective, despite significant efforts to move tick control strategies towards IVM, including the One Health approach (Dantas-Torres et al., 2012; Eisen and Dolan, 2016; Benelli and Duggan, 2018), tick control is still too anchored to the massive use of chemical acaricides. The development of new products with more eco-friendly features [see Ghosh et al. (2015) and Benelli et al., (2016b) for recent reviews] is lowered by several technical problems, with special reference to the lack of uniform methods to test toxicity on ticks among research groups, as

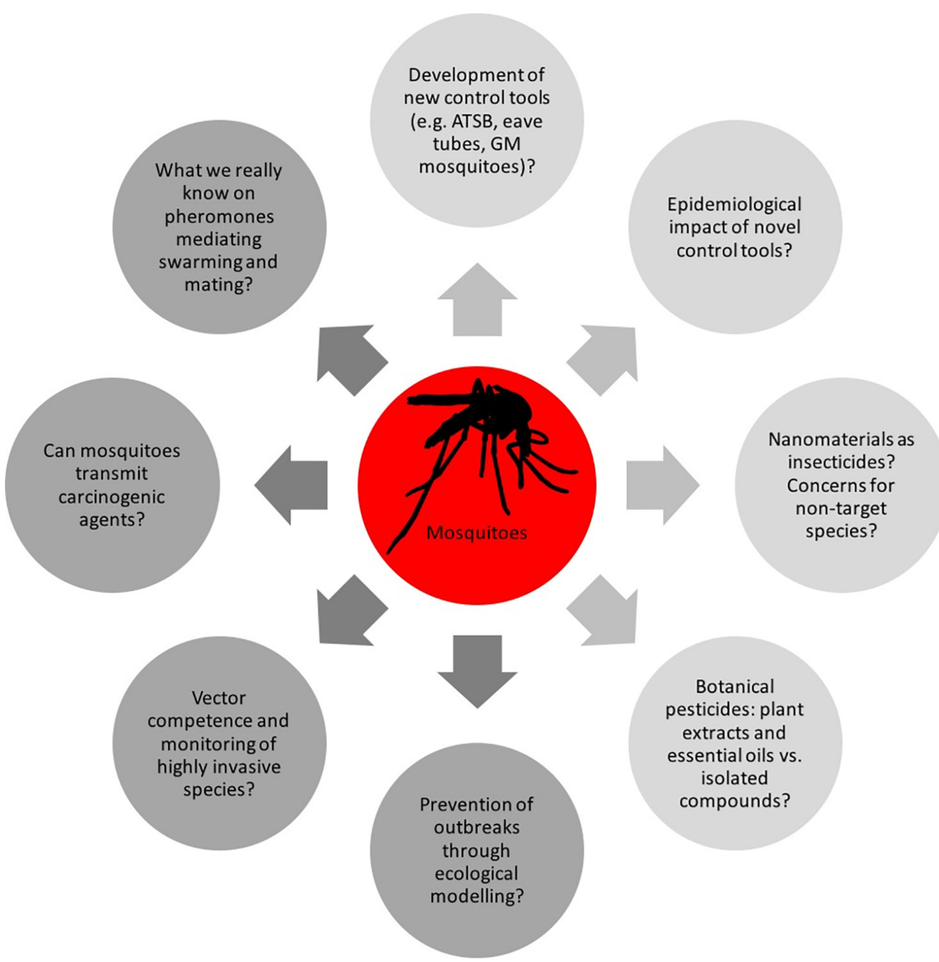

Fig. 3. A research agenda for next future mosquito research: key questions to address about mosquito biology and ecology are given in dark grey, while crucial issues about control tool development and validation are given in light grey.

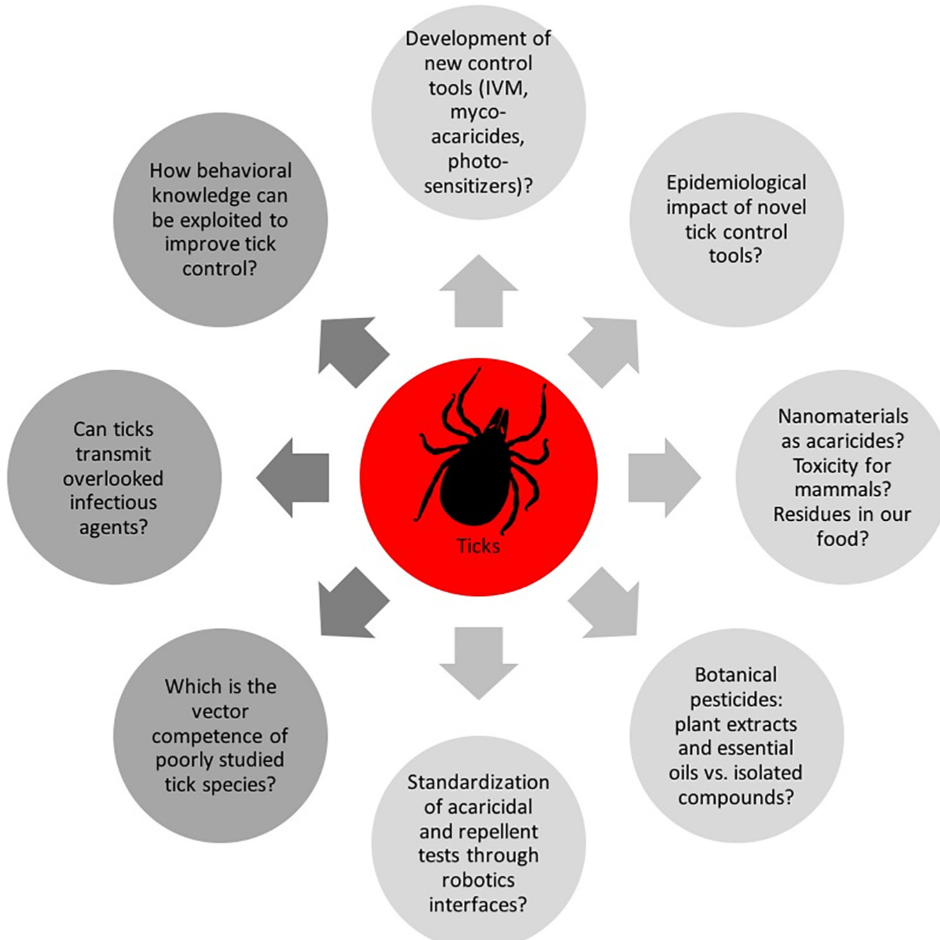

Fig. 4. A research agenda for next future tick research: key questions to address about tick biology and ecology are given in dark grey, while main issues about control tool development and validation are given in light grey.

recently pointed out in a systematic review by Benelli and Pavela (2018) as well as by Adenubi et al. (2018). In this framework, can robotics help us to standardize tick testing protocols (Romano et al., 2018)? A preliminary reply has been recently provided by a study developing a mechatronic device that may be used to repeatedly test repellents in association with selected host-borne cues over time (Benelli et al., 2018c).

Concerning biological control tools, it has been stressed the timely importance of basic studies to understand the interactions of entomopathogenic fungi with the components of the livestock skin microenvironment, since this would help to identify suitable fungal strains, and develop improved formulations (Polar et al., 2008).

Above, we referred to herbal preparations that can be used as acaricides and repellents against ticks. Some of these uses have a long ethnobotanical history, with a confirmed efficacy both in medical and veterinary settings (George et al., 2014; Ellse and Wall, 2014; Adenubi et al. 2016; Pavela et al., 2016). However, a long-standing unresolved question in this research field is: do we really need to isolate pure compounds from plants (Tabari et al., 2017)? Or is better and eco-friendlier to avoid further synthesis processes and use the selected whole plant essential oil or extract? In the first case, this allows to skip problems linked with the chemical composition of essential oils and extracts, which is subjected to strong variations according to many biotic and abiotic factors (Heng et al., 2013). However, the first solution is often more expensive and did not permit to exploit the synergistic toxicity effects that occur among the phytochemicals present in complex mixtures (Pavela, 2015a,b; Benelli et al., 2017c,d).

Nanoparticles and close-related nanomaterials have been tested – besides mosquitoes – also against selected tick species, achieving really interesting results (Benelli et al., 2017b). However, also in this case, there are some imperative questions to face. First, do nanoparticles represent a hazardous material for non-target species? Are they suitable to be used to fight ticks infesting livestock and pets? In this framework, which are the possible ecotoxicology implications for large mammals and soil invertebrates? Similar questions are relevant also about the use of photosensitizers as acaricides (Khater et al., 2016).

5. Conclusive remarks and future challenges

Overall, all the questions outlined above urgently need a further replies and research efforts from both public health experts, epidemiologists, parasitologists, biologists, and entomologists, as also recently pointed out by Stone et al. (2018) about research on plant-mosquito interactions, and by Benelli et al., (2018b) concerning the One Health approach in parasitology and ecotoxicology.

As highlighted by Fernandes et al. (2018a), a number of novel tools with a promising potential in arthropod vector control science are being developed. However, more efficient health system infrastructures and entomological capacity are urgently required in endemic countries to ensure an effective management of vector populations.

A research agenda for next future mosquito research is provided in Fig. 3. It summarizes – among the questions raised in the paragraphs above – some crucial ones. Furthermore, research agenda for next future tick research is given in Fig. 4. To my eyes, the future of mosquito and tick research is largely dependent from the close cooperation between various disciplines, since most of the current control tools being developed and later assessed in the field for their real-world efficacy needs a huge mixture of competences and analytical tools from many research fields. This is the case of insecticidal and acaricidal nanomaterials, which requires cooperation from the fields of physics, phytochemistry, as well as vector biology, physiology, behavior and ecology (Benelli, 2018b, c). Large networks of scientists with various research expertise, from molecular genetics to population ecology, are also needed for monitoring of invasive species, their DNA barcoding (Zhang and Zhang, 2014; Lv et al., 2014a,b; Murugan et al., 2016; Vadivalagan et al., 2017; Karthika et al., 2018), as well as the reliable evaluation of vector competence potential and molecular patterns of infection in different regions worldwide (Murdock et al., 2014; Vega-Rúa et al., 2014; de la Fuente et al., 2017; Bartholomay and Michel, 2018; Priya et al., 2017). New technology is needed for pathogen detection in bloodsucking arthropods. In this framework, Fernandes et al., (2018b) recently developed a rapid noninvasive detection tool to identify Zika virus in *Ae. aegypti* mosquitoes, relying to near-infrared spectroscopy.

In conclusion, I am aware that this review cannot fully reflect the high diversity of the ideas and new insights rapidly growing in the field of mosquito and tick research. Furthermore, I hope that it will contribute to boost research and applications on successful mosquito and tick control strategies, along with an improved knowledge about the impact of mosquito and tick biology and ecology, since the latter is limited, but still crucial to ensure proper success of vector control programs in an IVM perspective.

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Conflict of interest

The Author declares no competing interests.

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