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Review Article

Tick Microbiome Composition, Interactions and Molecular Detection: A Review

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Abstract

Ticks have been known to carry pathogenic organisms responsible for several diseases of livestock and humans. Together with pathogens, ticks also contain other microorganisms of various species, called endosymbionts. Knowledge on these endosymbionts and their role in transmission of pathogens by ticks however remains scant. This review aims to reveal those pathogens and endosymbionts that constitute the microbiome of ticks with a focus on tick species predominant in sub-Saharan Africa. The range of pathogens transmitted by ticks includes viruses, bacteria, and parasites. The diverse range of tick-transmitted bacteria includes the genera *Borrelia, Rickettsia, Ehrlichia, Anaplasma* and *Coxiella*. Ticks also harbour another group of symbiotic microorganisms that includes some *Rickettsia, Coxiella, Francisella* and *Wolbachia*. These symbiotic microorganisms have been found to have important roles in their host tick's development, reproduction, immunity and handling of environmental stress. Recent developments in metageniomics offer hope of better identification and understanding of tick microbiota. More knowledge on this subject can potentially help in reaching novel tick borne disease prevention and control methods by targeting the endosymbionts. In the long run, this might help lessen the burden of ticks and tick borne diseases on the livestock sector in sub-Saharan Africa.

Keywords: Ticks; Microorganisms; Endosymbionts; Microbiome; Sub-Saharan Africa

Introduction

Ticks are ectoparasites that feed exclusively on blood of vertebrate animals [1,2]. They transmit a wide range of pathogens that heavily affect human and animal health leading to serious medical issues [3] and highly significant economic losses in the livestock [4]. In addition to mortalities, the global losses in livestock production caused by ticks reach up to 14 billion US Dollars per year [2].

Ticks and the pathogens they transmit (tick-borne pathogens), have caused huge losses to farmers due to control efforts and mortalities. They also have a huge impact on human health. Ticks are widely distributed in the world including in sub-Saharan Africa, affecting up to 80% of the world's cattle population. Due to this big impact, ticks have been severely studied although symbiotic relationships with some microorganisms remain poorly understood [3]. The term microbiome refers to the broad group of commensal, symbiotic, and pathogenic microorganisms. For ticks, these include bacteria, viruses and other tick-borne pathogens [4]. The tick microbiomes play a big role in pathogen transmission [3].

Tick-borne pathogens are very diverse and belong to many genera such as *Rickettisia, Ehrlichia, Anaplasma, Borrelia* and *Coxiella* [5]. Of these, there are four main tickborne diseases that cause the huge losses to the livestock industry. These are theileriosis, babesiosis, heartwater and anaplasmosis [6]. Ticks also cause tick paralysis, anemia, reduced milk output and general loss of condition [6]. Furthermore, ticks transmit several pathogens of zoonotic importance. Cremean-Congo Heamorrhagic Fever (CCHF) caused by CCHF virus and several rikettsioses such as those caused by *Rickettsia africae* and *R. conorii* have been reported in Africa before [7]. Cremean-Congo Heamorrhagic Fever virus is transmitted mainly by ticks of the Hyalomma species while *Amblyomma* species transmit *R. africae* [8]. African tick bite fever, a disease caused by *R.africae* is now regarded as a leading re-emerging disease [9].

Ticks also harbor many non-pathogenic bacteria forming a symbiotic relationship that is beneficial to both. The relationship between these endosymbionts and pathogenic bacteria in ticks has been studied using electron microscopy [10] and recently next generation sequencing [9]. This new technology has led to more extensive studies on the relationships between ticks and their microbiome [9].

There is still room for further studies on the interactions of endosymbionts and pathogens in ticks. Such studies will need to expose the intrinsic link between endosymbionts and pathogens, and possibly bring out much needed new ticks and tickborne disease control strategies. To craft effective control intervention strategies, it is vital that the transmission dynamics of the pathogens and all compounding factors are well known and understood [4]. These factors include environmental and anthropogenic factors that determine rate of spread and abundance of ticks and pathogens they transmit.

Ticks of veterinary and medical importance in sub-Saharan Africa

Ticks are blood-feeding parasites under phylum Arthropoda, order Acari [11]. The main families are Ixodidae (hard ticks) and Argasidae (soft ticks) while the third family, Nuttalliellidae only has one species. Ticks are considered as the most important ectoparasites of livestock and known to be the most common arthropod vectors of disease to livestock worldwide [6].

There are seven and three genera of ixodid (hard ticks) and argasid (soft ticks) respectively in Africa [11]. The common genera of ixodid ticks in the tropics are *Amblyomma, Rhipicephalus* (including *Boophilus*) and *Hyalomma* [6]. The hard ticks spend most of their time on their host [11]. In contrary, argasid ticks have a relatively shorter feeding time and spend much of their time in their host's environment and housing [12]. *Argas*, *Otobious* and *Ornithodoros* are the three genera of veterinary significance among the argasids [11].

Many species of hard and soft ticks occur throughout sub-Saharan Africa acting as vectors of some very significant diseases of livestock and re-emerging zoonoses such as rickettsioses [7]. *Rhipicephalus (Boophilus) microplus* and *Amblyomma variegatum* are the two most common and widespread species of hard ticks in Africa [6]. Another ixodid tick species, *Rhipicephalus appendiculatus*, is responsible for transmission of theileriosis, a disease caused by *Theileria parva*, which causes severe losses due to mortalities and morbidities throughout east and central Africa [12].

Microbial composition of ticks

Microbiome is the collection of commensals, symbionts, mutualists and pathogens found in and on ticks [9,4]. These include communities of microorganisms such as bacteria, viruses and other eukaryotes. They potentially affect each other as they usually co-exist [1]. Tick microbiota are determined by several factors such as the environment, host genetics and presence and numbers of other microbial species. This means microbial species that are adapted to the same environmental conditions can co-exist within the same host [3]. The tick microbiome play an important part to the survival of the tick as they can determine its susceptibility to pathogens and also provide supplementary nutrients to their poor blood based diet [2]. This has been proven by studies which have shown ticks struggling in survival after treatment with antibiotics [13].

Endosymbionts have also been shown to be closely linked to some tick-borne pathogenic microorganisms of humans such as *Coxiella burnetii* [7]. In Palestine, pathogens and endosymbionts such as *Theileria, Bebesia, Bartonella* and *Rickettsia* were found in ticks collected from domestic livestock [2] while in Israel endosymbionts such as Francisella were found in *Hyalomma* ticks collected from livestock and migratory birds [2].

Pathogenic microorganisms found in ticks are in the form of protozoa, bacteria and viruses. They are of great medical and veterinary importance. Protozoa that are common in many hard ticks include those from the *Babesia* genus [6]. Babesia species belong to the family of Apicomplexa and they attack the vertebrate host's erythrocytes. *Babesia bovis* and *B. Bigemina* are transmitted mainly by Rhipicephalus ticks and cause huge economic losses in the livestock industry especially in the sub tropics .The ticks are infected by the protozoan parasites during a blood meal when they ingest blood which has [6] the parasite's piroplasms, which will develop into gametes in the tick's midgut [12]. Further development occurs in the tick's organs resulting in transovarian transmission in some of the species. The parasites are passed in tick saliva and infect the erythrocytes when the tick has attached onto a new host [13]. Another very important tick transmitted disease of cattle in sub-Saharan Africa is Theileriosis, also known as East Coast Fever [14]. It is caused by infection with *Theileria parva*, a hemoprotozoan parasite of the genus *Theileria*. The organisms are phylogenetically closely related to genus *Babesia*, order Piroplasmida [12]. Transmission occurs when an infected *Rhipicephalus appendiculatus* tick feeds on cattle and releases sporozoites along its saliva, which then go on to infect the lymphocytes and develop into schizonts [14].

Among the many viruses of public health and veterinary impact transmitted by ticks, Crimean Congo Heamorrhagic Fever (CCHF) virus has been widely studied. It is transmitted to humans by ticks of the *Hyalomma* species. After the tick takes a bloodmeal, the virus enters tick cells by endocytosis [1]. It replicates in the lining of the midgut and thereafter infects other organs of the tick including the salivary glands [8]. The CCHF virus causes a disease in humans characterised by headaches, fever and heamorrhagic tendencies [1].

Several species of bacteria are known to infect ticks. Infection of the ticks occurs after the tick feeds on a bacteremic animal or other means such as transovarial transmission [14]. Examples of bacteria that are transmitted by ticks are *B. burgdorferi*, the causative agent of Lyme disease and *Rickettsia africae* transmitted by ticks of the *Amblyomma* species*. Rickettsia africae* causes African Tick Bite Fever (ATBF), a re-emerging zoonoses common in sub-Saharan Africa [15]. Both Lyme disease and ATBF are zoonotic tick-borne disease in which the bacteria is maintained in domestic and wild animals with occasional spillover to humans after tickbites [14].

The interactions between ticks and their microbiome

Among the microbiomes, interactions results in many different relationships such as exclusive, competitive, facilitative and totally absent. These lead to different effects on animal and human health [16]. There is a gap in the understanding of tick endosymbionts with their role in pathogen transmission having been studied in a few species [7]. This is especially true for ticks of sub-Saharan Africa where not much has been documented regarding their microbial compositions. Probably the most studied endosymbionts, Coxiella–like endosymbionts, are the most vertically transmitted organisms in hard ticks [16]. Other endosymbionts are Rickettsia-like symbionts and Francisella-like symbionts that infect hard ticks from many genera. Some of these tick endosymbionts have evolutionary links to some tick borne pathogens such as Coxiella burnetti with Coxiella-like endosymbionts. Changes from pathogenic and symbiotic forms can occur from either form [7]. Francisella-like symbionts are thought to have evolved from the pathogenic forms of Francisella species [1]. Interactions between symbionts and pathogens have an effect on the quantities of the pathogen in the tick. An example is that of *Rickettsia bellii*, an endosymbiont that has been found to inversely affect the quantities of *Anaplasma marginale* in ticks [1]. Another example of relationships between symbionts and pathogens is the exclusion relationships seen in Rickettsiales which is thought to be due to cross immunity within the bacterial family [1].

One of the documented role of the non-pathogenic microbial community in ticks is their nutritional support to their host ticks. Ticks' diet is predominantly blood which makes them deficient in some nutrients such as the vitamin B complex. This weakness is countered by the symbiotic bacteria, as seen in Coxiella-like endosymbionts that encode for vitamins B2, B5, B6, B7 and B9 in *Amblyomma americanum* ticks [17]. The role of endosymbionts in promoting development and reproductive capabilities of ticks was shown in *Ornithodoros moubata* nymphs' failure to moult into adults in the absence of Francisiella endosymbionts after they were destroyed using antibiotics [18].

Ixodes ricinus, a hard tick widespread across Europe has been extensively studied because of its medical importance in the region [4]. The tick carries the pathogens of the genus Borrelia, the cause of Lyme disease [19]. Ticks collected from areas that are endemic for the disease have been found to be also infected with *Anaplasma phagocytophilum* and C*andidatus* Neoehrlichia mikurensis [20]. *Candidatus* Midichloria mitochondrii*,* an endosymbiont, was also found in majority of the collected female ticks [4]. It is thought that the endosymbiont has a helping role in tick mounting [1]. In the Masai Mara National Park, [10] found Coxiella-like endosymbionts in *Rhipicephalus*, *Amblyomma* and *Hyalomma* ticks. The same study found that the ticks were concurrently infected with the pathogens; *Anaplasma ovis*, *A. bovis* and *Theileria parva.*

Interactions between ticks and their microbiome are reported to sometimes take a three-way form between the tick, non-pathogenic microorganisms and the pathogens. Studies suggest that certain components of the gut microbiome of the tick, Ixodes scapularis (a vector for Lyme disease in North America), are key for the successful establishment of the pathogen, *Borrelia bugdoferi*, in the tick [21] although the underlying physiological mechanisms are not yet fully understood [22].

The effects of different environmental conditions on tick microbiome composition and interactions are still a subject of much study. It has been observed, during field studies, that the composition and structure of the tick microbiome is influenced by the ecological differences at regional level [16]. [22] suggests that differences in tick microbiome diversity in different areas is due to ticks getting the varied microbes that are present in the soils of their localities. Studies by [17] proved this suggestion although [23] could not find any link between tick microbiome variation and sampling sites.

Studies done on *Ixodes ricinus* in the Swiss Alps concluded that although factors such as gradient and elevation have a role in microbiota composition, it is the tick's microenvironment, its specific traits and microbial interactions (e.g., facilitation) within the tick which ultimately determines the composition of its endosymbionts and pathogens [19].

Recent advances in molecular detection of tick microbiome

The interactions between ticks and their microbiome are now better understood due to the recent increase in the use of next generation sequencing. The advent of next generation sequencing (NGS) has offered a new lease in the study and characterisation of pathogens and endosymbionts using metagenomics [24]. The term "next generation sequencing" simply refers to any high-throughput sequencing technology [4]. Its use has led to a better understanding of the tick microbiome composition and how the different microbes interact. This may eventually lead to the development of new tick and tick-borne disease control methods possibly by influencing the tick microbiome. This can be in the form of using microbes that decrease the survival of pathogens in the ticks leading to a decrease in tick borne diseases prevalence [25]. This high throughput technology has also exposed how complex the tick microbiome is [7].

Next generation sequencing was first used on tick microbiome by [26] on *Rhipicephalus (Boophilus) microplus* ticks (through the 454 pyrosequencing technique). Several bacteria in the genera *Coxiella, Wolbachia, Borrelia* as well as many species of Staphylococcus were identified [4]. Metagenomic sequencing of tick microbiome is not without its own challenges. One major challenge is on the efficient purification of the microbiome from the host. Poor purification can lead to inefficient sequencing as host sequences can "contaminate" the sequences, overriding the microbial sequences of interest. Therefore more sequencing runs will be needed to account for the dominated microbial sequences, resulting in higher costs [4]. A method that uses flow cytometry to separate cells based on size and fluorescent markers to exclude host cells and retain microbial cells has been developed to overcome this challenge. This not only helps characterise the tick endosymbionts that help nourish ticks, but also the load of the microbial communities in ticks [4].

Conclusion

The impacts of ticks and tick borne pathogens in the livestock sector, where they affect up to 80% of the world's cattle [27], and human health in sub Saharan Africa cannot be overemphasized. Despite the many studies that have been done on the subject, the role of the symbiotic microorganisms found in ticks remains a gap for further study. While in recent years several studies have been documented on microbiomes in ticks in Europe and elsewhere, not much has been done on the tick species predominant in sub-Saharan Africa. The report of *Coxiella* endosymbionts found in ticks in the Masai Mara National Reserve in Kenya by [10] shows that these symbiotic microorganisms are present in ticks in the various African ecosystems and warrant further investigations on how pathogen and endosymbiont interactions are affected by the different African environmental and farming setups. This will potentially aid our knowledge and guide practices with regard to tickborne disease control in Africa.

The role of endosymbionts in vector competence and pathogen transmission needs to be thoroughly investigated. The composition and interactions of microbiomes in ticks need more analyses as this offers hope of a realistic novel control method for tickborne diseases. The potential benefits of new tickborne disease prevention and control do not only help the livestock sector but also humans where tickborne zoonoses are now regarded as re-emerging medical threats.

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