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Review

Targeting a global health problem: Vaccine design and challenges for the control of tick-borne diseases

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ABSTRACT

It has been over twenty years since the first vaccines for the control of tick infestations became commercially available. These vaccines proved their efficacy and the potential of this approach for the control of tick-borne diseases (TBDs), which represent a growing burden for human and animal health worldwide. In all these years, research in this area has produced new tick-derived and pathogen-derived candidate protective antigens. However, the potential of vaccines for the control of TBDs has been underestimated due to major challenges to reduce tick infestations, pathogen infection, multiplication and transmission, tick attachment and feeding time and/or host pathogen infection. Nevertheless, vaccines constitute the most safe and effective intervention for the control of TBDs in humans, domestic and wild animals.

Contents

1. Introduction

Vector-borne diseases (VBDs) represent a growing burden for human and animal health worldwide [1–3]. Ticks (Acari: Ixodida) are obligate hematophagous arthropod ectoparasites that are second to mosquitoes as vectors of pathogens causing diseases in humans and the first cause of VBDs in farm animals [4]. Among the most prevalent tick-borne diseases (TBDs), Lyme disease caused by some species of the *Borrelia burgdorferi* sensu lato (s.l.) complex and anaplasmosis caused by *Anaplasma* spp. constitute a growing burden for humans, companion and farm animals worldwide [4–10] (Table 1).

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Table 1
Characterization of selected TBDs caused by TBPs with different transmission cycles.

TBP	TBD	TBD-affected hosts[a]	Main tick vector species	Tick cycle[b]	TBP transmission time at tick bite	Transovarial transmission
Bacteria						
B. burgdorferi s.l.	Lyme disease	H/C	*Ixodes* spp.	3	16–72 h	No
Anaplasma phagocytophilum	Human granulocytic anaplasmosis, tick-borne fever	H/F	*Ixodes* spp.	3	24–48 h	No
Anaplasma marginale	Bovine anaplasmosis	F	*Rhipicephalus* spp., *Dermacentor* spp.	1, 3	24–48 h	No
Anaplasma platys	Canine cyclic thrombocytopenia	C	*Rhipicephalus sanguineus*	3	16–72 h	No
Rickettsia rickettsii	Rocky Mountain spotted fever	H	*Dermacentor* spp., *Amblyomma* spp., *R. sanguineus*	3	10 h	Yes
Ehrlichia ruminantium	Heartwater	F	*Amblyomma* spp.	3	48–96 h	No
Protozoans						
Babesia divergens, Babesia microti	Human babesiosis	H	*Ixodes* spp.	3	48–72 h	Yes, No
B. divergens, Babesia bovis, Babesia bigemina	Bovine babesiosis	F	*Ixodes* spp., *Rhipicephalus* spp.	1, 3	48–216 h	No
Theileria annulata	Tropical theileriosis	F	*Hyalomma* spp., *Rhipicephalus appendiculatus*	3	48 h	No
Babesia canis, Babesia vogeli	Canine babesiosis	C	*R. sanguineus, Dermacentor* spp., *Haemaphysalis leachi*	3	48 h	Yes
Viruses						
Tick-borne encephalitis virus	Tick-borne encephalitis	H	*Ixodes* spp.	3	Immediate	Yes
Crimean-Congo hemorrhagic fever virus	Crimean-Congo hemorrhagic fever	H/F	*Hyalomma* spp.	3	Immediate	Yes
Louping ill virus	Louping ill	F	*Ixodes ricinus*	3	Immediate	No

Data compiled from de la Fuente et al. [4] and Schorderet-Weber et al. [10].
[a] TBD-affected hosts: H (human), C (companion animal), F (farm animal).
[b] The number of hosts involved in tick life cycle.

Several approaches have been implemented for reducing the risk of TBDs. These approaches include the use of chemical acaricides, which have been only partially successful and often accompanied by serious drawbacks including the selection of acaricide-resistant ticks and contamination of the environment and animal products with residues, the use of botanical acaricides and repellents, entomopathogenic fungi and the education about recommended practices to reduce exposure to ticks and available options for the management of drug resistance [11,12]. Additionally, integrated control programs that include habitat management and the genetic selection of hosts with higher resistance to ticks have been also proposed to reduce the use of acaricides for the control of tick infestations [11,12]. Recent developments have suggested the possibilities of combining chemicals with repellency and parasiticidal activity to reduce the risk of TBDs [10]. This approach intends to prevent both vector infestations and pathogen transmission [10]. However, major difficulties such as long-lasting effect and safety for human and animal use encourage the development of vaccines, which could induce a long-lasting protective immune response against vector infestation and pathogen infection and transmission [11].

Vaccines constitute one of the greatest advances in science with a substantial impact on improving human and animal health. Vaccines for the control of TBDs have been controversial due among other limitations to the impossibility of preventing tick infestations and consequently the possibility of pathogen transmission. For those involved in the development of vaccines for the control of tick infestations and TBDs, these limitations constitute a challenge that has been approached by developing new platforms for the identification and characterization of candidate tick-derived and pathogen-derived protective antigens [13,14]. As discussed in this paper, recent results support that vaccines are indeed the most effective and environmentally sound approach for the prevention and control of TBDs.

2. Current status of the vaccines for the control of TBDs

The first vaccines for the control of cattle tick infestations became commercially available in the early 1990s [15]. These vaccines contained the *Rhipicephalus microplus* BM86 or BM95 recombinant antigens and their use demonstrated that vaccines could constitute an effective component of the integrated programs for the control of TBDs [11,15,16]. These vaccines were not designed to prevent tick infestations, but to reduce tick populations and the prevalence of tick-borne pathogens (TBPs) by affecting feeding, reproduction and development of ticks feeding on immunized animals and ingesting with the blood meal antigen-specific antibodies that interact with and affect protein function [11,15,16]. Most of the data available on vaccine efficacy against tick infestations under field conditions have been obtained in cattle [11,15,16], but results are also available in other farm animals such as sheep and camels, companion animals such as dogs, and natural wild tick hosts such as deer [7,11]. Vaccines based on tick-derived antigens have also shown to have an effect on reducing pathogen infection and transmission with the possibility of targeting multiple tick species and other arthropod vectors [11,17]. Finally, the use of pathogen-derived antigens has proven effective for reducing the risk of Lyme disease under certain conditions in both humans [18] and natural reservoir hosts [19,20], but currently due to safety issues, commercial vaccines are not available for this disease [18]. Among TBDs for which vaccines are currently available, tick-borne encephalitis (TBE) caused by TBE virus (TBEV) is one of the most widespread in Europe [21,22]. An inactivated virus vaccine also provides partial protection against Louping ill virus (LIV) and Spanish goat encephalitis virus (SGEV) in sheep [23]. For other tick-borne viruses such as Crimean-Congo hemorrhagic fever virus (CCHFV) causing the CCHF, the efficacy of vaccines based on inactivated virus has not been clearly demonstrated [22].

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