Ticks and Tick-borne Diseases xxx (2014) xxx–xxx

Contents lists available at ScienceDirect

Ticks and Tick-borne Diseases

journal homepage: www.elsevier.com/locate/ttbdis

Review Article

Towards a genomics approach to tick (Acari: Ixodidae) control in cattle: A review

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ARTICLE INFO

Article history:
Received 9 January 2014
Received in revised form 7 April 2014
Accepted 8 April 2014
Available online xxx

Keywords:
Bos taurus africanus
Host genetic resistance to ticks
Single-nucleotide polymorphisms
Tick control
Genomic selection

ABSTRACT

Ticks and tick-borne disease (TBD) are major challenges to cattle production in the tropics and subtropics. Economic losses associated with ticks amount to billions of dollars annually. Although efforts to eradicate ticks and TBD using chemical control strategies have been implemented in many developing countries for decades, these acaricides are costly, and cattle susceptibility to ticks remains unchanged. Traditional breeding methods, where the farmer selected animals using records to improve the host genetic resistance to ticks (HGRT), are less than fully effective and time consuming. The HGRT has been reported in literature. To date, solutions to fight ticks and TBD are still unclear. Development of single-nucleotide polymorphism (SNP) technologies has created an opportunity to estimate breeding values of animals from DNA samples. The use of SNP technology for genomic selection allows information retrieval from the genotype even before the gene is expressed; thus potentially giving farmers the ability to make selection decisions on HGRT at an earlier age. This review discusses factors that affect HGRT, breeding selection, immunology, and genomic approaches and their application to improve HGRT in order to enhance livestock production.

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http://dx.doi.org/10.1016/j.ttbdis.2014.04.006
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Please cite this article in press as: Mapholi, N.O., et al., Towards a genomics approach to tick (Acari: Ixodidae) control in cattle: A review. Ticks Tick-borne Dis. (2014), http://dx.doi.org/10.1016/j.ttbdis.2014.04.006

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Introduction

There is greater demand for animal protein worldwide, especially with the increasing affluence in the emerging markets of Brazil, Russia, India, China, and South Africa. This has led to increased consumption of beef and dairy products and necessitated an expansion of global cattle production. Ticks are a major challenge to increased cattle production affecting an estimated 1.4 billion cattle worldwide (FAO, 2011). On a global basis, ticks are one of the most important vectors of disease pathogens in livestock and companion animals (Ghosh et al., 2006). Tick-borne diseases (TBD) result in huge economic losses in both dairy and beef production systems, especially in tropical and subtropical areas (Rajput et al., 2006). Direct effects of tick infestation on cattle include the sucking of blood which causes anaemia and damage to the skin or hide, with downstream effects resulting in reductions in fertility, body weight, and milk production, and in toxicoses, paralysis, and mortality (Turton, 2001; Jongejan and Uilenberg, 2004; Kaufman et al., 2006).

Conventional tick control is based on application of acaricides. The use of these acaricides has increased the incidence of acaricide-resistant ticks and exacerbated the occurrence of environmental and food contamination (Parizi et al., 2009). Together, these problems generate a rising economic and social demand for alternative approaches to reduce tick infestation and thereby enhance the contribution of cattle to the world economy. Natural immunity, developed by cattle in environments where ticks are endemic, shows promise for genetic tick control strategies which will reduce expenditure on acaricides and other chemical control methods (Frisch, 1999; FAO, 2004). Tick control strategies targeted at the host's immunity require that immunity can be assessed using an appropriate and accurate method.

Mapping of the bovine genome has opened new avenues for determining the genetic basis for host genetic resistance to ticks (HGRT), using technologies such as single-nucleotide polymorphisms (SNPs) and copy number variants, and thus enabling their control in cattle (Piper et al., 2008). The current review discusses the distribution of common tick species, their economic impact on cattle production, and their control. Host resistance to ticks, breed variability in susceptibility to tick infestation, classic breeding and selection approaches to reducing susceptibility or increasing tolerance to ticks, as well as genomic tools to improve resistance are also discussed.

Geographical distribution of common ixodid ticks in Africa

Tick species distribution in Africa

There are approximately 879 known tick species worldwide. These species are grouped into 3 families: Argasidae or soft bodied ticks (186 species), Ixodidae or hard bodied ticks (692 species), and Nuttalliellidae (1 species) (Navas et al., 2009). The present review focuses on ixodid ticks, as they have devastating impacts on cattle. In Africa, there are over 650 tick species belonging to 7 genera. Of the 7 genera of hard-bodied ticks that affect livestock in Africa, 3 are of economic importance in cattle (Table 1). These are: *Rhipicephalus* (including the new subgenus *Boophilus*), *Amblyomma*, and *Hyalomma* (Sonenshine, 1991; Walker et al., 2003; Jongejan and Uilenberg, 2004).

Factors affecting tick distribution

Broad-scale factors that limit the ranges of tick species have not been definitively established. Given that most tick distributions are not limited by those of their host species, it can be inferred that a primary factor preventing expansion of tick species ranges is a direct effect of climate (Cumming, 2002). Olwoch et al. (2009) suggested that if global warming leads to temperature increases, the incidence of ticks will further increase in regions where ticks are endemic. This could have serious implications for seasonal variation in tick infestation, TBD incidence, and TBD control strategies. In South Africa, for example, increased environmental temperature is thought to have caused displacement of the indigenous African species *Rhipicephalus decoloratus* by the Asiatic intruder *Rhipicephalus microplus* (Tønnesen et al., 2004; Nyangiwe et al., 2013). Except for extremely cold and dry areas, *R. microplus* has extended its range and is now present in all warm and humid areas of the country. The bont tick (*Amblyomma hebraeum*) was reported to occur only in the warm, moist coastal areas of South Africa (Coetzer et al., 1994). However, it has recently been reported that *A. hebraeum*'s distribution is expanding to the inland semiarid areas of South Africa (Nyangiwe et al., 2011). The expansion in distribution of the bont tick in South Africa may be associated with more intense periods of drought especially in the inland highlands areas as hypothesised by Estrada-Peña et al. (2008) for the bont tick in Zimbabwe.

The distribution and abundance of ticks are also impacted by factors other than climate such as presence of alternative hosts,

Table 1
Common tick species in Africa, their life cycle, and pathogens transmitted by them.

Tick species	Life cycle	Pathogens transmitted
Amblyomma hebraeum	Three-host	*Ehrlichia ruminantium*
Rhipicephalus decoloratus	One-host	*Babesia bigemina* *Anaplasma marginale*
Rhipicephalus microplus	One-host	*Babesia bovis* *Babesia bigemina* *Anaplasma marginale*
Rhipicephalus appendiculatus	Three-host	*Theileria parva*
Rhipicephalus evertsi evertsi	Two- or three-host	*Anaplasma marginale*

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Table 2
Estimated annual economic losses due to ticks and tick-borne diseases.

Country	Cost in US$	References
Global	7 billion	McCosker (1979)
Global	13–18 billion	de Castro (1997)
Africa	160 million	Dold and Cocks (2001)
Ethiopia	1.5 million	Newson (1991)
South Africa	92 million	Farmer's weekly (1998)
Brazil	2 billion	Grisi et al. (2002)
Australia	184 million	Playford et al. (2005)
India	498.7 million	Minjauw and MacLeod (2003)

natural resistance, acaricide use, and grazing management (Cumming, 2002). In situations where the natural hosts of ticks are sparsely distributed, alternative hosts tend to gain importance in influencing tick distribution. For example, in Zimbabwe, the only factor favouring the survival of the tick *A. hebraeum* in the low veld habitats where cattle densities are low is the presence of alternative wildlife hosts (Norval et al., 1994). Alternative hosts also act as vehicles for moving ticks between distinct habitats further increasing their distribution (Ruiz-Fonsa and Gilbert, 2010). Intensive acaricide treatments over long periods coupled with the absence of alternative hosts may also alter tick distributions (Norval et al., 1994). These factors need to be considered when mapping the distribution of ticks and in prediction of the future distribution of ticks. As ticks continue to expand their range into previously uninhabited areas, outbreaks of TBD are also likely to increase negatively impacting cattle production. Additional or updated tick surveys need to be conducted to cater for these tick distributional dynamics.

Economic impact of ticks and tick-borne diseases on cattle production

Estimation of the economic impact of ticks and tick-borne diseases on cattle production

Apart from causing diseases, ticks cause substantial losses in terms of reduced productivity and fertility and often death, and are economically the most important ectoparasites of cattle (Rajput et al., 2006). The lack of accurate data on the epidemiology of ticks and TBD makes it difficult to determine their impact. Table 2 shows the estimated costs of ticks and TBD to cattle production in different countries. Although a fairly crude estimate, these values may help to comprehend the importance of ticks and TBD of cattle. These estimates expose the need for more studies on the determination of the economic impact of ticks and TBD on the cattle industry, especially in developing countries.

Losses due to tick infestations

Each tick bite causes stress and weakens the host's immune responses which affect the performance of the animals. The economic losses due to ticks can be expressed either in terms of body weight or milk production lost per engorged tick or in terms of average financial loss (production loss plus cost of control) per animal per year (Jonsson, 2006). Each engorging *R. microplus* tick female causes the loss of 8.9 ml of daily milk production and 1.0 g of body weight in high-yielding Holstein-Friesian cows (Jonsson et al., 1998). The loss of 14% production rate of the lactation would result in a significant reduction in income and would be particularly a serious loss for livestock-dependent systems (McLeod and Kristjanson, 1999).

Losses due to tick infestation are breed-dependent with *Bos indicus* cattle being least affected, *Bos taurus* being severely affected, and their crosses having intermediate losses proportional to the level of *Bos indicus* genes (Jonsson et al., 2008). Breed-specific losses appear to result from breed differences in susceptibility to infestation. In South Africa, Scholtz et al. (1991) indicated that every engorged female *R. decoloratus* tick causes a reduction of 8.9, 8.0, and 8.6 g in the weaning masses of calves from Hereford (*Bos taurus*), Bonsmara (*Bos taurus africanus* × *Bos taurus* crosses) and Nguni (*Bos taurus africanus*) cows, respectively. However, the observed minor effect of infestation on the productivity of the Nguni cows was small due to their natural resistance. Norval et al. (1988) estimated losses of up to 4 g of body weight per engorging adult *Rhipicephalus appendiculatus* tick in *Bos taurus* steers. Sanga (*Bos taurus africanus*) cattle were observed to suffer less severe losses.

The damage caused by tick bites also diminishes the value of skins and hides for the manufacture of leather. Tick bite marks are among the different factors causing the non-availability of good quality raw material for the leather industry, causing between 20 and 30% depreciation in normal value in the market (Biswas, 2003). It has been assumed that hide damage is a function of the number of ticks infesting cattle and is probably independent of breed (Jonsson, 2006). Ticks with a long hypostome may induce abscesses because of secondary bacterial infection which in turn attracts myiasis-producing flies, further compounding the arthropod-related problems for cattle producers (Ghosh et al., 2006).

Economic impact of ticks and tick-borne disease treatments

A large component of the economic costs of ticks in cattle is the application of control measures to reduce infestations (de Castro, 1997; Porto Neto et al., 2011). Conventional tick control is based on the application of acaricides. There are few global reports on the costs involved in tick control and TBD treatments. Expenditures for tick control were estimated at US$ 8.43, 13.62, and 21.09 per animal per year for plunge dipping, hand spraying, and pour-on, respectively (D'haese et al., 1999). The mean annual cost of ticks and TBD control per animal in pastoral and ranch herds was estimated to be US$4.54 (Ocaido et al., 2009). There is a need for more studies on the losses associated with tick and TBD control to ensure the accurate estimation of the total cost of these parasites on cattle production. The major component of economic costs of TBD, which can constitute up to 88% of total costs, is on their control (Ocaido et al., 2009). The control of TBD can be a large and regular part of the variable cost of beef farming in most infested areas, with control measures mainly involving a combination of acaricide and grazing management, together with a slowly growing interest in immunisation (Minjauw and MacLeod, 2003).

Losses due to tick-borne diseases

Besides the losses due to the direct effects of ticks and their control, significant losses also arise indirectly due to the important role of ticks in the transmission of TBD. The economic impact due to TBD can be substantial, especially in cases of sudden outbreaks in susceptible herds. Losses that can be directly attributed to TBD are mortality, chronic morbidity, costs of veterinary diagnosis and treatment, costs of vaccines, and costs arising from restrictions on movement of cattle (Jonsson et al., 2008). Tick-borne diseases can cause downgrading of live animals at sales, and of meat, offal, and hides (Tisdell et al., 1999). Introduction of more tick-resistant cattle substantially reduces the costs associated with ticks and TBD. This is due to lowered manifestation of TBD, because fewer ticks are likely to attach per day due to reduced numbers of ticks in the field and because a smaller proportion of ticks that do develop to feed on infected cattle will in turn be infected (due to lower parasitaemia) (Jonsson et al., 2008). There is a need for the investigation of alternative control measures that are effective, safe, and economically and environmental acceptable (Webb and David, 2002). One such

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control measure is development of cattle that are resistant to tick infestation and (or) TBD.

Tick control

In regions where ticks are endemic, control methods include treatment with acaricides, pasture rotation, environmental modification, and integrated biological and chemical control management programmes.

Chemical tick control

Globally, chemical control has been the main strategy to combat tick infestations. The practice of intensive tick control spread rapidly throughout Africa following the introduction of imported cattle breeds and, in most southern African countries, it was enforced through legislation. Use of acaricides in many developing countries is becoming more expensive (de Castro and Newson, 1993). In tropical and subtropical countries, the control of TBD in susceptible exotic cattle breeds still depends on intensive tick control using acaricides. However, regular dipping to prevent tick infestation and TBD infections is a costly exercise for the farmer as it results in increased veterinary and labour costs, possible tick resistance to acaricides, and unnecessary animal movement and handling (Jonsson, 2006).

In Africa, intensive dipping and spraying programmes using acaricides have been ineffective in eradicating ticks and TBD. This is due to poor management of acaricides and improper legislations. For example, in Zimbabwe as a result of the civil war from 1973 to 1978, dipping services were interrupted in the communal areas with disastrous consequences (Norval, 1979). About one million head of cattle died of TBD. These deaths were most likely caused by a lack of immunity, resulting from cattle previously being too effectively dipped, and the natural disease challenge and maintenance of enzootic stability being disrupted. Small-scale farmers use complimentary treatments including hand picking, household disinfectants such as Jeyes fluid, and used car oil to control ticks (Masika et al., 1997; Moyo and Masika, 2009). Most of these practices are not desirable in terms of animal and human health. One of the biggest problems with acaricide use in tick control is the selection of chemical-resistant tick strains which evolve faster than the development of new chemicals for tick control (Regitano and Prayaga, 2010). Moreover, many cattle breeds still remain susceptible due to the lack of predictability of TBD endemicity and misinformation about natural exposure. In addition, the use of acaricides increases the production costs and also leaves chemical residues in meat, milk, hides, and the environment (Machado et al., 2010). There is a growing public demand for residue-free animal products (Regitano et al., 2008), and an integrated approach to tick control utilising alternative tick control methods is thus needed to reduce overdependence on acaricides and address the issue of residues in meat.

Tick vaccines

Vaccination with tick antigens is a safe alternative to the use of acaricides to control ticks in cattle (Kimaro and Opdebeeck, 1994). Vaccines are potentially important in the control of disease agents, mainly for not being chemical agents, for being cheaper, and because development of tick resistance against vaccines is slower than against acaricides (Willadsen, 1997). Commercial tick vaccines for cattle based on the *Boophilus microplus* Bm86 gut antigen have proven to be a feasible tick control method that offers a cost-effective, environmentally friendly alternative to the use of acaricides (de la Fuente et al., 2007). Tick vaccines reduce the number of engorging female ticks, their weight and reproductive capacity, meaning that the greatest vaccination effect is seen as a reduced larval infestation in the subsequent generation (Willadsen, 2006). The delay in the 'knock down' effect of tick vaccines is the principal reason why vaccine use is often coupled with limited acaricide application for short-term control of unacceptable tick burdens. The major disadvantage of some of the tick vaccines in current use is that they may not offer protection against multiple tick species. However, controlled immunisation trials conducted by de Vos et al. (2001) indicated that the *R. microplus* BM86-containing vaccines protect also against other tick species. Tick infestation is rarely a one-species issue, and therefore, tick vaccines should aim at a broader protection against the main species of economical and epidemiological interest.

Grazing management

Pasture rotation combined with acaricide application is one economical method for controlling ticks on beef cattle, and it reduces tick densities on a large scale. Areas with good vegetation and high rainfall, however, produce more ticks than those with poor vegetation and erratic rainfall. Pasture burning can also be used to effectively control ticks as it significantly reduces tick populations on pasture (Spicket and Fivaz, 1992). Annual pasture burning reduces tick loads on cattle (Baars, 1999). In some instances, however, tick eggs hatching can miss the effect of fire while hiding in the soil surface suggesting that pasture burning alone may not be an effective tick control method (Young et al., 1988). Another alternative technique to reduce ticks and TBD is to eliminate wildlife hosts of particular species from the livestock environment. For example, the separation of buffalo from cattle in Kenya reduced tick burdens and incidences of TBD in cattle (Young et al., 1988). The same principle was used for *Ixodes scapularis* and white-tailed deer (Stafford et al., 2003).

Mechanisms of resistance to ticks in cattle

Natural resistance

The use of naturally tick-resistant cattle biotypes may be incorporated in tick control schemes as a means of biological control of tick infestations (Tatchell, 1992). An understanding of the biological intricacies underlying vector–host–pathogen interactions is required to innovate sustainable tick management strategies that can ultimately mitigate the impact of animal and zoonotic tick-borne diseases (Brake and Perez de Leon, 2012). Studying the mechanisms of resistance to ticks among different breeds of cattle may contribute to the development of alternative control methods (Gasparin et al., 2007).

Morphological coat traits

Tick infestation is affected by several innate morphological coat traits, most of which have high heritability (Regitano and Prayaga, 2010). Exhibition of coat characteristics that are unfavourable for tick attachment is an important mechanism of resistance to tick infestation in cattle. Phenotypic coat characteristics such as hair length, coat thickness, coat smoothness, and coat colour have an influence on tick counts and are related to HGRT in cattle on rangelands (Martinez et al., 2006; Foster et al., 2007; Marufu et al., 2011; Ibelli et al., 2012). Cattle with short, smooth, and light-coloured coats tend to have lower tick counts compared to those with long, rough, and dark-coloured coats (Verissimo et al., 2002; Gasparin et al., 2007). Short and smooth hairs make it difficult for ticks to attach and easier for animals to groom themselves while

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dark-coloured hairs act as a camouflage thus protecting ticks against predators, such as birds (Martinez et al., 2006).

Cutaneous hypersensitivity responses and cellular immunity

Cutaneous hypersensitivity reactions to tick antigens also influence host resistance to ticks (Kemp et al., 1986). The development of a strong cutaneous delayed-type hypersensitivity (DTH) reaction to ticks has been associated with increased HGRT in cattle (Bechara et al., 2000; Piper et al., 2010; Marufu et al., 2013). The lack of a DTH in susceptible animals has been attributed to tick saliva-induced suppression of protective immune responses during infestation (Ferreira et al., 2003; Brossard and Wikel, 2004). Apart from humoral responses, several cell types are thought to influence acquired resistance to ticks in cattle (Gill, 1984; Latif et al., 1991). Basophils and mast cells appear to be the major effectors of acquired resistance at tick feeding sites in cattle. A vigorous granulocyte response especially in the earlier stages of infestation has been reported to be characteristic of the immediate-type hypersensitivity reaction responsible for tick rejection in tick-susceptible taurine cattle (Latif et al., 1991). An abundance of mononuclear cells, basophils, and eosinophils is characteristic of a delayed-type hypersensitivity reaction at tick feeding sites on the skin of highly resistant hosts after repeated infestations (de Castro and Newson, 1993; Szabó and Bechara, 1999).

Mast cells and the histamine they contain inside cytoplasmic granules are of fundamental importance for the self-grooming mechanism, which is thought to be critical for resistance of cattle to ticks (Verissimo et al., 2008). Resistant bovines have a greater capacity than susceptible hosts to retain eosinophils in the lesion of adult tick-infested skin (Carvalho et al., 2010). Eosinophils are thought to be involved in the translocation of mast cell histamine to the tick attachment site resulting in increased grooming and tick rejection in cattle (Francischetti et al., 2009). Constantinoiu et al. (2010) observed the presence of consistently higher numbers of T cells in the resistant *Bos indicus* cattle and suggested that these cells might have a role in resistance to infestation. This was supported by the report of Piper et al. (2009) that tick-resistant *Bos indicus* cattle develop a T-cell-mediated response to infestation which is absent in the *Bos taurus* cattle. Comparison of immune responses of resistant and susceptible cattle is thus a good strategy in the identification of candidate genes associated with resistance (Bram, 1983; Drummond, 1983; Peter et al., 2005). Factors affecting host responses to ticks should always be borne in mind during such comparison studies.

Host resistance, breeding and selection to increase host resistance

Factors affecting host genetic resistance to ticks

Several factors such as morphological, physiological, and behavioural traits influence the resistance of cattle to ticks. Host body size affects tick abundance, with larger-bodied animals being more heavily infested with ticks than smaller-bodied ones, due to a greater surface area for tick infestation in the former. Morphological coat traits have been discussed earlier (Marufu et al., 2011) and influence HGRT in cattle. Heifers and cows are thought to be more resistant to ticks than bulls, and this could be attributed to testosterone, which reduces both innate and acquired resistance to tick feeding (Hughes and Randolph, 2001). Pregnant cows are more susceptible to ticks that non-pregnant cows due to the immunosuppressive effects of gestational hormones in the former. Younger animals carry fewer burdens of ticks than older animals (Swai et al., 2005), due to continuous selective grooming behaviour in the younger animals (Fivaz and de Waal, 1993). Preferential grazing in areas with shorter grass and less bush is a form of tick avoidance behaviour which may help to increase resistance to ticks in cattle (Meltzer, 1996).

Breed variability for host resistance

Resistance to ticks is also known to be under genetic control. The genetic basis for variation in HGRT, within and among breeds, has been recognised for many years (Wilkinson, 1955; Francis, 1966). *Bos indicus* (Zebu) cattle such as the Brahman are regarded to be generally more resistant to ticks than *Bos taurus* (European) cattle breeds such as the Angus and Hereford (Utech et al., 1978; Madalena et al., 1990; Frisch and O'Neill, 1998; Wambura et al., 1998; Bianchin et al., 2007; da Silva et al., 2007). European breeds (*Bos taurus*) were observed to carry up to 2.5 times more ticks than *Bos indicus* cross cattle under natural conditions (Seifert, 1971). Indigenous African cattle breeds (*Bos taurus africanus*), such as the Afrikander and Nguni, have also been shown to be more resistant to ticks than imported and local crossbred cattle (Scholtz et al., 1991; Fivaz et al., 1992). In the Gambia, the N'Dama (*Bos taurus africanus*) breed was shown to possess a higher degree of resistance than Gobras and N'Dama × Gobra crosses against adult *Amblyomma variegatum*, *Hyalomma truncatum*, and *Hyalomma marginatum rufipes* ticks (Mattioli et al., 1993; Mattioli and Dempfle, 1995). Much progress has already been made in crossbreeding to improve the productivity of tick-resistant cattle breeds in countries like Australia and Brazil (Utech and Wharton, 1982; Frisch et al., 2000). Moreover, backcrossing has been effective in introgression of desirable resistance traits into susceptible breeds. The Senepol composite beef breed was developed by crossing Red Poll and N'Dama and has shown increased HGRT when compared to other pure taurine breeds (O'Neill et al., 2010).

There is an increasing role for crossbred bulls in developing countries to combine the desirable attributes of various breeds while maintaining a high degree of HGRT and environmental adaptation. Several studies quantify the level of HGRT in different cattle breeds against specific tick species (Table 4). In beef cattle production, problems with low resistance in exotic breeds can be avoided by crossing them with high-resistance indigenous breeds. This can be only considered if productivity traits increased at the same level as that achieved by crossing to indigenous cattle.

In dairy production systems, the situation is far more complex than in beef production. Milk yield of the tropical breeds is much lower compared to that of the temperate dairy breeds. In Brazil, Furlong et al. (1996) reported a 23% reduction in milk production when Gyr (*Bos indicus*) bulls were crossed with Holstein (*Bos taurus*) dairy cows to increase HGRT. The F_1 progeny was moderately resistant to ticks and had reduced milk production (Furlong et al., 1996). The major challenge in dairy systems is that semen is obtained from donor bulls in temperate countries. These bulls have not been subject to either artificial or natural selection for resistance to tick infestation. This results in crossbred progeny with only moderate resistance to ticks. It may be concluded that there is likely to be a serious challenge in crossbreeding with Holstein to achieve resistance to ticks without sacrificing milk production.

Heritability estimates for host resistance to ticks

Heritability estimates of host resistance (average = 0.27) are summarised in Table 3. The host genetic resistance to ectoparasites is thus thought to be approximately as heritable as milk yield or growth, and resistance to ticks may be increased to very high levels by selection.

Low tick infestations in cattle and use of tick scores instead of tick counts could result in the lowering of heritability estimates

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Table 3
Heritability estimates of tick resistance.

Cattle breed	Location	Challenge	Tick trait	Heritability	Reference
Shorthorn	Australia	Natural/artificial	Count	0.39	Wharton and Roulston (1970)
Nguni	South Africa	Natural	Count	0.26	Schoeman (1988)
Caracu	Brazil	Natural	Count	0.22	Fraga et al. (2003)
Hereford Shorthorn line	Australia	Natural	Count	0.44	Henshall (2005)
Holstein × Gir	Brazil	Artificial	Count	0.21	Peixoto et al. (2008)
Bonsmara	South Africa	Natural	Count	0.17	Budeli et al. (2009)
Brahman	Australia	Natural	Score	0.15	Prayaga et al. (2009)
Gir × Holstein (F_2)	Brazil	Artificial	Count	0.21	Machado et al. (2010)
B. taurus breeds (dairy herds)	Australia	Natural	Count	0.37	Turner et al. (2010)

(Prayaga and Henshall, 2005; Prayaga et al., 2009). Genetic variation in host resistance between cattle increases as natural infestation increases under extensive conditions (Budeli et al., 2009). In Australia, the Illawarra Shorthorn (*B. taurus*) dairy breed was selected for HGRT (Utech et al., 1978). Further, Utech and Wharton (1982) indicated that there is potential to select for higher resistance within the breed through culling animals that are susceptible to ticks. Frisch et al. (2000) developed a Hereford × Shorthorn (*B. taurus*) line of cattle that had high resistance. However, it was suggested that the high level of host resistance in this line of cattle was due to a single major gene, but this was later confirmed not to be the case (Henshall, 2004). Even in the Nguni breed which is generally considered resistant to tick infestation, Mapholi et al. (2013) observed significant variation in tick counts and repeatability across months of 0.22 (unpublished observation). Despite the generally moderate degree of additive genetic variation observed within various breeds implying scope for selection and a limited number of examples of the efficacy of selection for resistance to ticks, inability to accurately measure the trait of interest has hindered application of genetic evaluation systems (Regitano and Prayaga, 2010). It should be noted that selection for resistance to ticks should not hamper improvement in other productive traits such as growth, meat quality, and milk yield. Several studies have reported low and non-significant genetic correlation between tick count and various productive, adaptive, and pubertal traits, and confirm that selection for HGRT may not have any unfavourable effects on other economically important traits (Davis, 1993; Prayaga et al., 2009) (Table 4).

Resistance of Holstein cows has been estimated in mid-lactation using artificial infestation with tick larvae, and selection for resistance was found to be effective without compromising milk production (Jonsson et al., 2000). Recent findings of Turner et al. (2010), using genome-wide association study with 10k SNP markers, also indicate that selection for resistance to ticks would not affect milk production. However, the innate level of tick susceptibility in Holstein cattle might limit the initial response to selection as any favourable alleles are likely to be in low frequency. Thus, opportunities for selection may be insufficient as cattle with high resistance to ticks and high milk production would be quite rare (Turner et al., 2010).

Molecular approaches to improve host resistance

Difficulty in identifying animals with high or low resistance to ticks is a major limitation to traditional selection based on phenotype. Thus, molecular genetic approaches seem indicated as an alternative approach for making selection decisions.

Candidate genes

Many economically important traits in livestock production are complex traits controlled by many genes. We hypothesise that resistance to infestation by ticks is one such trait. However, only a few of these many genes may have substantial effects. The first significant association between tick load and serum amylase phenotypes was identified in the late 1960s on bovine chromosome 3, and it was confirmed that cattle with serum amylase C are less infested than other genotypes (Ashton et al., 1968). Later, acute-phase protein components of innate immune responses were also evaluated and found to explain the differences between susceptible and resistant breeds of cattle Holstein (*B. taurus*) to Nelore (*B. indicus*) animals under natural conditions (Carvalho et al., 2008). The results from these studies confirmed that the difference in serum concentration of some proteins (e.g. haptoglobulin and transferrin) and could be potentially used as biomarkers to monitor the level of tick infestation.

In the early 1980s, the bovine leucocyte antigen (BoLA) group was identified and found to be associated with tick load. The detection of BoLA markers was done in microlymphocytotoxicity tests using different composite breeds under natural and artificial tick infestations (Stear et al., 1984, 1989, 1990). Although these studies confirmed the mapping of resistance alleles to the bovine major histocompatibility complex (MHC) locus, the results were not consistent, because the same BoLA allele was not always associated with increased HGRT. Following the BoLA marker findings, DNA microsatellite markers were selected as Class II BoLA microsatellite polymorphisms and were found associated with the susceptibility of three quarter Taurine cattle to *B. microplus* (Acosta-Rodriguez et al., 2005). In addition, an association was also found between BoLA marker-DRB allele 3.2, 18, 20, and 27 for lower tick numbers in a reference Holstein × Gyr F2 population in Brazil (Martinez

Table 4
Cattle breeds and their level of resistance to specific tick species.

Cattle breeds	Level of resistance	Tick species	References
Brahman compared to Hereford	High	*Rhipicephalus microplus*	Rechav (1987)
Nelore compared to Taurine breeds	High	*Rhipicephalus microplus*	Gomes et al. (1988)
Nguni compared to Hereford & Brahman	High	*Rhipicephalus decoloratus*	Rechav et al. (1991)
Zimbabiansanga compared to Nguni and Brahman	High	*Amblyomma variegatum*, *Rhipicephalus decoloratus*	Norval et al. (1996)
Boran compared to Tulis	High	*Rhipicephalus microplus*	Frisch and O'Neill (1998)
Gobra Zebu compared to N'Dama	Low	*Amblyomma variegatum*, *Hyalomma*	Mattioli and Dempfle (1995)
Jersey compared to tropical breeds	Low to average	*Rhipicephalus* sp., *Amblyomma* sp., *Hyalomma* and other African multi-host ticks	Utech et al. (1978), Spckett and De Klerk (1989), Norval et al. (1996), Solomon and Kaaya (1996)

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et al., 2006). Another significant association with tick numbers were found in DRB1 and DBR3 (Untalan et al., 2007). These findings confirmed the location of genetic variation affecting host resistance to ticks on bovine chromosome 23 (BTA23).

The results from gene expression profiles obtained after tick challenge on resistant versus susceptible cattle give promise on an alternative method of identification of candidate genes. A study by Wang et al. (2007) using cDNA microarrays describes 66 genes with differential expression in tick-challenged skin of resistant versus susceptible Adaptaur cattle. Among these genes, type I, III, and V collagen genes showed higher expression in resistant animals than in susceptible animals, and Keratin genes were more suppressed after challenge in susceptible than in resistant animals. These results suggest that some of the genetic variation of HGRT can be explained by genes related to skin structure.

Quantitative trait loci (QTL)

Several studies have identified QTL associated with particular phenotypes, including immunity in livestock production. Identified QTL that affect economically important traits including resistance to ticks are available on the QTL database (www.animalgenome.org). In Brazil, a *Bos taurus* × *Bos indicus* F_2 population was developed from 1999 to 2005 by Embrapa, and 382 individuals were measured for tick load (scoring and count). From 382 F_2 animals, microsatellite panels were used to scan all chromosomes for QTL for tick load, and positive associations were found on chromosomes 2, 4, 5, 7, 10, 11, 14, 18, and 23 (Gasparin et al., 2007; Regitano et al., 2008; Machado et al., 2010). All detected QTL were dependant on the season in which the phenotype was measured. In total, all the above QTL mapped on the 382 F_2 animals explained 13.1% of phenotypic variation in the rainy season and 18.4% in the dry season. The only QTL significant in both seasons was detected on BTA23 (Machado et al., 2010) in the genomic region also containing the BoLA genes which had been previously known to be associated with tick burden. Machado et al. (2010) also fine mapped the QTL on BTA 10 and BTA 11 reducing the confidence interval associated with the QTL. However, the results were not clear enough to identify a potential candidate gene associated with host susceptibility or host resistance to ticks due to the large size of the QTL region.

Genome-wide association studies (GWAS)

Development of genetic technologies, such as high-density SNP panels, provides an opportunity to evaluate individual animals based on their genotype. Knowledge of the location of loci linked to genes causing a variation in traits of economic importance can be exploited to increase effectiveness of selection (Georges et al., 1995), given an appropriate reference population for training a prediction equation that quantifies the relationship of genotype and phenotype (Meuwissen et al., 2001). This genome scan approach has been used effectively for complex traits where several genes are likely to contribute to the variability (Schnabel et al., 2005; Williams, 2005; Machado et al., 2010).

Recently, a GWAS found scores of SNPs significantly ($P < 0.001$) associated with tick burden (Turner et al., 2010; Porto Neto et al., 2011). A QTL for tick burden was identified on BTA3 in the region of the BoLA marker from previous studies. Further 13 chromosomal locations were identified associated with tick load. Turner et al. (2010) using a 10k SNP panel found a low correlation between the allele effects for milk composition and tick burden further suggesting that selection based on markers used to increase HGRT might not cause an undesirable response in milk traits. The majority of markers explained a small proportion (~1%) of the phenotypic variation. The studies of Porto Neto et al. (2010, 2011) complemented the previous studies with additional markers located in the same genomic regions. The markers were analysed for associations with tick burden as single markers and as SNP haplotypes. However, both initial QTL on BTA3 and BTA10 were confirmed in dairy and Brahman cattle, and the QTL intervals were reduced and the Integrin Itga11 candidate genes were also identified (Porto Neto et al., 2010, 2011). The location of a QTL affecting tick burden on BTA10 was close to the ITGA11 gene position, when using 17 SNP panel from BTA10 in Brahman and taurine cattle. Barendse (2007) using SNP assay, reported that several genes influencing the immune system are linked to HGRT.

Conclusion

An understanding of the mechanisms behind genetic resistance to ticks and tick-borne diseases (TBD) in livestock species could improve breeding programmes to develop animals that are more resistant and productive. Genetic variation in resistance of livestock should be quantified within and across breeds so that appropriate strategies are adopted in breeding programmes. For breeds with moderate to high resistance selection based on an index that combines breeding values for resistance and production traits will achieve desirable results; however, in low-resistance breeds, introgression of major genes would be the way to improve these breeds within a reasonable time period. The development of a genetic marker panel and high-density SNP chips has provided an opportunity to evaluate individual animals based on their DNA genotype. The application of marker-assisted selection and genomic selection promises great benefits since conventional breeding for resistance to ticks and tick borne diseases by analysing tick counts and scores (phenotypes for resistance) in a large number of animals is not practical in commercial breeding schemes. Genome-wide association studies are opening a way to identify SNPs of interest within the population. The host and tick genomics and their proteomics, such as gene expression profiles, are likely to facilitate studies addressing the sequencing, annotation, and functional analysis of their entire genomes. This could provide valuable information for improving tick control.

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Please cite this article in press as: Mapholi, N.O., et al., Towards a genomics approach to tick (Acari: Ixodidae) control in cattle: A review. Ticks Tick-borne Dis. (2014), http://dx.doi.org/10.1016/j.ttbdis.2014.04.006