14 Ticks and Tick-Borne Diseases in Cattle

LUCIANA CORREIA DE ALMEIDA REGITANO¹
AND KISHORE PRAYAGA²

¹Embrapa Southeast Cattle, São Carlos, São Paulo, Brazil; ²CSIRO Livestock Industries, Rockhampton, Australia, current address: CSIRO Livestock Industries, Queensland Bioscience Precinct, St Lucia, Australia

Summary
Ticks and tick-borne diseases are of global importance, affecting livestock, human and companion animals. In particular, cattle ticks are responsible for severe economic losses in the tropics, with costs associated with parasite control along with losses in fertility, body weight and milk production. Ticks are also vectors of a variety of pathogens, with babesiosis, theileriosis and anaplasmosis being important diseases transmitted by ticks. While chemical control with acaricides has been a main tick control strategy, inadvertent selection of acaricide-resistant tick strains, which evolve faster than development of new chemicals, is a major cause for concern. Thus, exploiting host genetic resistance has a great potential to complement other control strategies and reduce the need for chemical control. Considerable variation both between and within breeds has been observed for tick resistance, with well-documented evidence of greater resistance of Bos indicus breeds compared to Bos taurus breeds. Tick load is affected by several genetically controlled morphological traits, such as coat colour and hair type, as well as genes related to the immune response. Within-breed heritability estimates vary from very low to high, depending on the evaluation method and the extent of parasite challenge, with mean values close to 0.3. Although this implies ample scope for selection, trait measurement remains difficult. Consequently, genetic markers would assist in selection under extensive farming conditions. For this purpose, quantitative trait loci (QTL) studies have been undertaken with results reported in this chapter. Tick-borne diseases are a more complex problem than ticks themselves, with resistance to such diseases not as well documented as resistance to ticks. In general, B. indicus cattle are more resistant to tick-borne diseases, with some evidence of variability in resistance to babesiosis and theileriosis. In summary, breeding for genetic resistance is potentially a promising means to control ticks, although the same cannot yet be stated for tick-borne diseases. Large efforts are currently being made in Australia and Brazil to develop genetic markers for tick resistance and to develop tick vaccines.
Introduction

Ticks and tick-borne diseases are of global importance because of their economic and health implications in livestock, human and companion animals (Jongejan and Uilenberg, 2004). An earlier study estimated the global cost of ticks and tick-borne disease control to be US$7 billion (McCosker, 1979). Since then there have been several reports on economic costs of specific tick-borne diseases indicating that the earlier report is an underestimate (Jongejan and Uilenberg, 2004). Cattle ticks are responsible for severe economic losses in both dairy and beef cattle enterprises in the tropics (Jonsson, 2006). The main economic impacts of ticks are the costs involved with parasite control along with losses in fertility, body weight and milk production.

The direct effects of tick parasitism are weight loss, anaemia as well as secondary infections in the parasite fixation site. Cattle tick (Rhipicephalus (Boophilus) microplus) has a preferential distribution in areas with high temperature and humidity, and is widely spread in the tropics. Although it is difficult to quantify the economic losses related to tick parasitism, there are some estimates available in the literature. Losses with tick infestations in Brazil were estimated to be on the order of US$800 million/year (Martinez et al., 2006). Furlong et al. (1996) estimated a 23% reduction in milk production in cross-bred Gyr (Bos indicus) × Holstein (Bos taurus) cows, which are considered to be moderately resistant. In cross-bred B. taurus × B. indicus beef cattle, Bianchini et al. (2007) estimated that treating animals with acaricides would increase their average final weight gain by 13 kg, compared with animals who received only anthelmintic treatment. The annual global costs associated with ticks and the diseases that they transmit to cattle amounted to US$13.9–18.7 billion (de Castro, 1997). In Australia, cattle tick is distributed around the northern coastal areas as far south as the Queensland–New South Wales border, where it is held by a quarantine boundary at an annual cost of c.AU$7 million (White et al., 2003).

Ticks are also vectors of a variety of pathogens that are implicated in severe pathologies in many mammalian species (De La Fuente et al., 2008). In cattle, babesiosis, theileriosis and anaplasmosis are some of the important diseases transmitted by ticks. Recovered animals normally remain tolerant, especially where these diseases are endemic (endemic stability). However, these diseases impair cattle production in developing countries and are especially harmful in areas where ticks are not present during all seasons of the year (enzootic instability).

Chemical control has been the main strategy to overcome tick infestations, but costs associated with treatment are considerable. In addition to the price of chemicals, indirect costs include reduced feed intake due to individual sensitivity to acaricides and from animal management factors. Animal stress from management is particularly critical in extensive production systems, in which chemical control sometimes involves moving animals across long distances to dipping facilities (Jonsson, 2006). Still, the most critical concern with the use of acaricides in tick control is the selection of chemical-resistant tick strains, which evolve faster than the development of new chemicals for tick control.
For example, there were concerns that strains of cattle ticks in Queensland developed resistance to all of the acaricides used for cleansing cattle before transportation (Kemp et al., 1999). Other concerns are the impacts on environment and human health due to the presence of chemical residues in animal food products.

Vaccines have also been proposed for tick control. The first commercial recombinant vaccine (Bm86) against R. microplus was released in 1995 (Willadsen and Jongejan, 1995). Even though this vaccine had a desired effect in reducing the number of engorging female ticks and controlling their reproductive capacity, it was widely recognized that it had relatively small impact on practical control of ticks owing to scientific and commercial reasons (Willadsen, 2006). While the idea of biological control with natural predators of ticks such as ants, mites, birds, parasitoid wasps, fungi and nematodes is also appealing and showed some promise (for detailed review, see Samish and Rehacek, 1999; Jonsson and Piper, 2007), issues such as manufacture and stability of the living agents in the field need to be resolved before it can be applied on a large scale (Willadsen, 2006). Given this scenario, exploiting host genetic resistance is an alternative that, in combination with other tick control strategies, has a great potential to reduce the need for chemical control. In this chapter, an attempt is made to summarize the current state of knowledge with regard to host resistance to ticks and tick-borne diseases in the tropical world, with special emphasis on its implications on cattle farming.

### Host Resistance to Ticks

#### Behavioural, morphological, physiological and environmental aspects of tick resistance

Tick load is known to be affected by several morphological traits, most of which have a highly inherited pattern, such as coat colour, hair type, hair thickness and hair length. Physiological status, such as age and pregnancy, are also determinants of the level of resistance throughout the lifetime, as well as environmental factors, mainly temperature and humidity, that affect the exposure to the parasite as well as parasite survival in the host. Grooming behaviour may also play an important role in the success of a host in eliminating parasites.

Compared to cohorts, darker-coloured animals are more susceptible to ticks than lighter-coloured ones (Fraga et al., 2003; Gasparin et al., 2007), females are more resistant than males, pregnant cows are less resistant than non-pregnant ones and younger animals are more resistant than older ones (Utech et al., 1978; Silva et al., 2009).

A relationship between hair phenotype and tick susceptibility has been observed in several experimental datasets. In a natural infestation survey of c.700 Caracu cows, a Brazilian creole B. taurus breed, Fraga et al. (2003) reported a greater number of engorged parasites in animals with thicker hair. The association between hair morphology and number of ticks was also described in a Holstein × Gyr F₂ generation population in Brazil, in which
animals with long curly hair had twice more ticks than those with short straight hair (Gasparin et al., 2007).

Madalena et al. (1985) examined causes of variation in tick burdens under natural infestation and found slightly higher correlations between counts in the same animals when both counts were made in spring/summer ($r = 0.40$) or in autumn/winter ($r = 0.39$), compared with counts made in different seasons ($r = 0.24$). Level of infestation affected these correlations, with the maximum value at around the mean tick burden (185 ticks per animal). When the levels of infestation were too low or too high the correlations between counts decreased.

**Immunological aspects of resistance to ticks**

Ticks and tick-borne pathogens engage in complex interactions with their mammalian hosts involving interplay between the defensive responses and counter-responses of host, tick and pathogen. These complex interactions are being unravelled by the advances in genomics leading to the novel means of parasite control targeting the tick–host–pathogen triangle (Jongejan, 2007).

To succeed in their life cycle, ticks need to spend a long period attached to the host, ranging from several days to weeks. Blood feeding during this period stimulates haemostatic, inflammatory and immunological responses in the host in an attempt to eliminate the parasites or to impair parasite development. Both regulatory and effector pathways of the host immune response are stimulated, and it has been demonstrated that consecutive infestations result in increased resistance (Wagland, 1978). Despite that, immunity to one species of tick does not assure protection against other species, as demonstrated by Miranpuri (1989) in cross-bred cattle infested by *R. microplus* and *Hyalomma anatolicum anatolicum*.

To understand the host response to ticks one needs to consider that tick saliva has evolved to produce a mixture of molecules that act as immune modulators, destroying tissue integrity and blocking host haemostatic cascades (Singh and Girschick, 2003; Brossard and Wikel, 2004; Ribeiro et al., 2006). In general, tick salivary gland extract (SGE) down-regulates the immune system. This effect is well described in many tick–host models and it is expected to be a relatively long-lasting effect, since it has been demonstrated that SGE is present in the skin for up to 5 days after larvae infestation (Allen et al., 1979). Among the targets of SGE immune modulators are the dendritic cells. Maturation of these cells is impaired when they are exposed *in vitro* to *Ixodes ricinus* saliva. *In vivo*, dendritic cell migration from the bite site on the skin to draining lymph nodes is reduced (Skallova et al., 2008).

Genetic variation for tick resistance results from differences in a variety of mechanisms that are not fully understood, yet involvement of genes related to the immune system in many of these mechanisms is undeniable. Therefore, comparison of the immune profile in resistant versus susceptible breeds has been the major strategy to elect candidate mechanisms to explain resistance. For instance, acquired resistance is developed earlier and reaches a higher level in resistant
than in susceptible breeds (Wagland, 1978). Although the exact mechanisms that lead to this difference are not clear, it is possible that they may include evading the inhibitory effects of tick saliva on the host’s immune response.

For example, Turni et al. (2002) demonstrated that lymphocytes from resistant *B. indicus* were less affected *in vitro* by the inhibitory effect of tick SGE than lymphocytes from susceptible *B. taurus*. Kashino et al. (2005) reported higher levels of IgG1 and IgG2 in Nelore animals heavily exposed to ticks, compared to susceptible Holstein. However, differences in IgG levels resulted mainly from a pronounced suppression of anti-tick saliva IgG antibody responses in Holstein rather than from an increase in IgG secretion in Nelore. Acute-phase proteins, components of innate immune responses, are also implicated in differences between susceptible and resistant breeds of cattle (Carvalho et al., 2008).

In some instances down-regulation of the immune response seems to be advantageous for the host. When cytokine mRNA levels were examined at the extremes of tick resistance in four genetic groups, down-regulation of interleukin 8 (IL8) was observed at the resistant extreme of the cross-bred ½ Angus, ½ Nelore group (Regitano et al., 2008). IL8 is a leukocyte chemoattractant protein that controls movement of leukocytes to the infection site, besides acting in the stimulation of angiogenesis. The relative advantage of inhibiting IL8 for the host’s defence is unclear. It is curious that this cytokine is inhibited by the salivary extract of several tick species (Hajnická et al., 2001), which leads one to consider that the inhibition would be beneficial to the parasite. Interestingly, *IL8* down-regulation was observed only in Angus × Nelore cross. Among the crosses studied, this was the only one sired by a British breed in that study. This finding suggests that specific mechanisms of host–parasite interactions were perpetuated in some breeds and not in others, possibly as a result of genetic drift during the establishment of breeds.

Other evidence of this breed-specific pattern of host-parasite interaction was given by Piper et al. (2008), who found differences between expression profiles of skin collected from the tick attachment site versus non-attachment sites in Holstein but not in Brahman. Field observations also support the idea that a variety of host mechanisms must be involved in blocking the parasite cycle, since some resistant individuals within the same experimental group develop a severe cutaneous reaction while others do not. Some have a great number of undeveloped nymphs attached to the skin while others have no parasites of any stage.

**Between- and within-breed variability for tick resistance**

Despite the complexity of tick–host interaction, there is a genetic component of variation in host resistance to ticks. This genetic variation is expected to be under the control of multiple genes if we consider all the mechanisms involved in resistance that vary from inherited differences in morphological traits to genetically determined variation in the immunological response to parasites, as discussed in previous sections.
The clearest difference in tick resistance among cattle breeds is the one between *B. taurus* and *B. indicus*, with the latter being several times more resistant (Lemos *et al*., 1985). In Brazil, higher resistance in *B. indicus* compared with *B. taurus* was first reported by Villares (1941). Later, Lemos *et al.* (1985) found an exponential relationship between tick burdens under heavy natural infestations and the Holstein–Friesian proportion in crosses with the Guzerat breed (*B. indicus*). Comparisons between sprayed and non-sprayed artificially infested cows revealed a 25% reduction in milk yield of mature non-sprayed Holstein–Friesian cows, while no difference in yield was observed in infested versus sprayed F1 or 5/8 Holstein–Friesian × Guzerat crosses (Teodoro *et al*., 1998).

The effect of *B. indicus* genotype on resistance is consistent among different crosses. For example, under relatively mild natural challenge, Teodoro *et al.* (1994) did not find differences in tick burdens among cross-bred progeny of Holstein, Jersey and Brown Swiss sires at the same *B. indicus* gene fraction. In tropical Australia, the use of tick-resistant *B. indicus* cattle and their crosses had been widely practised over the years. Utech *et al.* (1978) reported a comprehensive study assessing tick resistance as determined by the percentage of larval ticks that failed to survive maturity following artificial infestations with tick larvae in various breeds of beef and dairy cattle. In beef cattle, not surprisingly, Brahmans were found to be more resistant than British cattle. In dairy breeds, *B. taurus* Jersey cattle were reported to be more resistant than Guernsey, Australian Illawara, Shorthorn and Friesian but not significantly different from cross-bred Australian Milking Zebu.

Recently, Prayaga (2003) reported breed group differences with significantly (*P < 0.05*) lower tick counts in Zebu-derived breed group (predominantly Brahmans) compared to Sanga-derived (Belmont Red–Africander × Hereford–Shorthorn cross) and tropically adapted British breed group (Belmont Adaptaur × Hereford–Shorthorn cross). In this Australian cross-breeding study, it was reported that as the Zebu proportion in the cross increased, the number of engorged ticks decreased. Further, Frisch and O’Neill (1998) also reported that Brahmans record slightly decreased growth rate when untreated for ticks and worms, but they still exceed the growth rate of British breeds under low to moderate natural parasite challenge in tropical climates of northern Australia. This further supports the genetic advantage of tropically adapted *B. indicus* breeds and their crosses over *B. taurus* breeds. Prayaga (2003) also reported significantly negative (favourable) breed additive component of the Zebu breed for tick counts suggesting their genetic resistance. A significantly negative (favourable) direct dominance effect between taurine × indicine breed crosses further supported the significant heterosis (−40%) reported in crosses involving Zebu and British breed group crosses in this study.

Genetic variation is also seen within a breed. Heritability estimates varied from very low to high (Alencar *et al*., 2005). This broad variation is attributed to evaluation method (artificial × natural challenge) as well as to the additive genetic variation for resistance, which is intrinsic to each population studied (Table 14.1). Further, differences in heritability also reflect the extent of natural parasite challenge under extensive conditions, enabling the expression of variation in tick resistance across various studies. Artificial challenge is more
efficient in controlling the environment variance, since during the free-living stage of a tick’s life cycle they are very sensitive to temperature, humidity and species of grass and, as pointed by Madalena *et al.* (1985), the correlations between counts in the same animal may be low if counts are made in different seasons. A mean of $0.34 \pm 0.06$ for the estimated heritability across breeds was reported in a review by Davis (1993). Despite the generally moderate heritability estimates across various breeds implying a scope for selection, one difficulty lies with the trait measurement hindering application in traditional genetic evaluation systems.

### Breeding for Host Resistance to Ticks

**Exploring genetic resistance in breeding programmes**

Selecting for increased host resistance is a low-cost and highly effective way of addressing the economic aspects of tick control. There have been several strategies to achieve this under field conditions. One of the effective ways to tackle the problem of cattle ticks has been the use of breeds or strains of cattle.

#### Table 14.1. Estimates of heritabilities of tick infestation from literature.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Location</th>
<th>Breed*</th>
<th>Trait</th>
<th>Challenge</th>
<th>$h^2$(s.e.)$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wharton <em>et al.</em></td>
<td>Australia</td>
<td>Shorthorn</td>
<td>Count</td>
<td>Natural and Artificial (sires)/</td>
<td>0.39</td>
</tr>
<tr>
<td>(1970)</td>
<td></td>
<td></td>
<td></td>
<td>Natural (Progeny)</td>
<td></td>
</tr>
<tr>
<td>Madalena <em>et al.</em></td>
<td>Brazil</td>
<td>Cross-bred</td>
<td>Count</td>
<td>natural</td>
<td>0.20 (0.06)</td>
</tr>
<tr>
<td>(1985)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mackinnon <em>et al.</em></td>
<td>Australia</td>
<td>AX, AXBX</td>
<td>Count</td>
<td>natural</td>
<td>0.34 (0.05)</td>
</tr>
<tr>
<td>(1991)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Burrow (2001)</td>
<td>Australia</td>
<td>AX, AXBX</td>
<td>Count</td>
<td>natural</td>
<td>0.44</td>
</tr>
<tr>
<td>Henshall <em>et al.</em></td>
<td>Australia</td>
<td>AX, AXBX</td>
<td>Count</td>
<td>natural</td>
<td>0.42</td>
</tr>
<tr>
<td>(2001)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fraga <em>et al.</em></td>
<td>Brazil</td>
<td>Caracu</td>
<td>Count</td>
<td>Natural</td>
<td>0.22</td>
</tr>
<tr>
<td>(2003)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fraga <em>et al.</em></td>
<td>Brazil</td>
<td>Caracu</td>
<td>Score</td>
<td>Natural</td>
<td>0.15</td>
</tr>
<tr>
<td>(2003)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Henshall (2004)</td>
<td>Australia</td>
<td>HS</td>
<td>Count</td>
<td>natural</td>
<td>0.44</td>
</tr>
<tr>
<td>Prayaga and</td>
<td>Australia</td>
<td>AXBX</td>
<td>Count</td>
<td>Natural</td>
<td>0.13 (0.03)</td>
</tr>
<tr>
<td>Henshall (2005)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peixoto <em>et al.</em></td>
<td>Brazil</td>
<td>Holstein × Gir</td>
<td>Count</td>
<td>Artificial</td>
<td>0.21 (0.12)</td>
</tr>
<tr>
<td>(2008)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prayaga <em>et al.</em></td>
<td>Australia</td>
<td>Brahman</td>
<td>Score</td>
<td>Natural</td>
<td>0.15 (0.10)</td>
</tr>
<tr>
<td>(2008)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*HS–F$_5$, Hereford–Shorthorn (*B. taurus*) cross, BX–F$_5$, Brahman (*B. indicus*) × HS, AX–F$_5$, Africander (Sanga, a tropically adapted taurine breed) × HS, F$_{3+}$ AXBX, a cross of AX and BX. $^b$Standard error, whenever available.
that are relatively resistant, for example Brahmans in Northern Australia. Further, cross-breeding has also been effective in introgressing desirable resistance attributes into a susceptible breed.

However, it is important to be mindful of the correlated responses in other economic traits such as growth, meat quality or milk yield as a consequence of selection for tick resistance. In Australia, several studies have reported low and non-significant genetic correlations between tick counts and various productive, adaptive and pubertal traits (Davis, 1993; Prayaga et al., 2009), indicating that the selection for tick resistance may not have any deleterious effects on other economic traits. However, caution needs to be exercised in selection programmes, particularly those using genetic markers, and research needs to be continued to screen for any associated effects on other economic traits.

In an attempt to develop a tick-resistant British line of cattle, a Hereford–Shorthorn line (Belmont Adaptaur) was selected in Australia for tick resistance over several generations (Frisch et al., 2000). It was reported that a genetic trend of a linear reduction in tick count, at the rate of 7 ticks/year, was achieved, reducing tick counts from a mean of 275 ticks/animal/day in 1983 to about 40 ticks/animal/day in 1998. Owing to this selection, a correlated response in weight (1.28 kg/year at 18 months of age) was achieved in this experiment and the authors argued that this increased weight was due to genetic improvement in tick resistance as no direct selection was applied for growth potential. Prayaga and Henshall (2005) reported low and non-significant genetic correlations between growth traits and tick counts, suggesting that selecting for growth under tropical conditions is unlikely to improve tick resistance at a genetic level. This was observed despite the fact that there was a significant increase in post-weaning live weight gain in animals treated for ticks and worms compared with the untreated control group (Prayaga, 2003).

In Brazil, evaluation of tick resistance was applied to a conventional progeny testing programme of dairy B. taurus × B. indicus sires. Tick resistance was scored after artificial infestation in young bulls, before semen collection. In addition, progeny were scored for tick burdens under natural infestation (Madalena, 1999). Culling the 10% most infested Holstein–Friesian heifers was predicted to reduce total infestation by 18%. This reduction increased to 26% when B. indicus represented three-fourths of the cross with Holstein–Friesian heifers. However, a decrease in correlation between counts of the same animal across time could lead to lesser benefits. Heritability and repeatability of log count of ticks per animal were 0.49 and 0.62, respectively. Genetic correlations of this trait with milk, protein and fat yields were low (0.06, −0.14 and 0.07, respectively).

Commercial expected progeny differences (EPDs) for tick burdens are currently estimated and utilized in Braford and Brangus (5/8 Aberdeen Angus, 3/8 Nelore) breeding programmes in Brazil (http://www.gensys.com.br/). The evaluations are conducted under natural infestation by the methodology described in Cardoso et al. (2006), in which tick counts are made in only one region of the body, the inner hind legs.
Finding genes and markers for tick resistance

Genetic variation in tick resistance both within and across breeds should, in principle, enable successful implementation of selection programmes. However, recording tick counts is not economical and not even feasible under extensive farming systems, highlighting the importance of developing genetic markers. While some pathways involved in resistance to cattle tick are known, little is known on how variation at specific loci contributes to the degree of resistance. Several efforts have been made in an attempt to isolate and validate markers for the selection of resistant genotypes, and these will be discussed in this section.

The first reports on markers for tick resistance were studies on blood protein polymorphisms (Francis and Ashton, 1967; Ashton et al., 1968; Panepucci et al., 1989). In all the studies, the serum amylase locus was associated with tick number. Curiously, few other investigations on this association were reported afterwards.

Frisch (1994) reported a Hereford–Shorthorn line of cattle selected for tick resistance under tropical conditions in Australia to be apparently segregating for a major gene for tick resistance. However, later studies found little support for a major gene, indicating that resistance attributes are more likely due to polygenic effects (Henshall, 2004). The obvious candidate genes for association with tick resistance are the genes for immune modulators and effectors. Associations between bovine major histocompatibility complex (MHC) (BoLA) class II alleles and tick resistance have been reported (Stear et al., 1990; Acosta-Rodríguez et al., 2005). An association between BoLA alleles DRB3.2*18, *20 and *27 and lower tick number was found in a reference Holstein × Gyr F2 population in Brazil (Martinez et al., 2006). In a study of natural infestation, genotypes for a microsatellite marker close to the IL4 locus were associated with tick number in cross-bred B. taurus × B. indicus and in pure B. indicus (Regitano et al., 2008).

Genomic scans for quantitative trait loci (QTL) controlling tick resistance are presently being undertaken in a reference F2 family in Brazil. In this project a Holstein × Gyr population of 382 F2 animals was developed from 1999 to 2005. The F2 generation was evaluated for tick resistance by experimental challenge during two seasons, as described in Gasparin et al. (2007). QTL detected to date have been dependent on the season when the parasite load was scored, which could be interpreted as a QTL–environment interaction. A total of five QTL were mapped for the trait scored during the rainy season and three for the same trait scored in the dry season (Regitano et al., 2008). More recently, two additional QTL were detected in this population, explaining 7.1% of the phenotypic variability observed during the dry season (Peixoto et al., 2008). In total, the QTL mapped in this resource population explained 13.1% of the phenotypic variation during the rainy season and 18.4% of the phenotypic variation in the dry season (Table 14.2). Half of the QTL mapped in that resource population deviate from the pure additive genetic model, which is in agreement with the heterosis found in crosses between B. taurus and B. indicus. It is also in agreement with the observed dominant behaviour of tick resistance in those crosses.
With the newly available bovine SNP chips, high-density SNP genotyping is the most promising strategy for fine-mapping these QTL and for functional SNP (quantitative trait nucleotide (QTN)) detection. Once detected, these tick resistance QTN would need to be validated for use in marker-assisted selection in other populations. The progress being made in this regard is evident from a recent report of an SNP assay for detecting tick resistance in cattle (Barendse, 2007). This study reported several genes from the immune system as being linked to tick resistance, although the MHC was not one of them.

Results from gene expression profiles obtained after a challenge of resistant versus susceptible animals are a good source of candidate genes for tick resistance. Recent work by Wang et al. (2007) described at least 66 genes with differential expression in tick-challenged skin of resistant versus susceptible B. taurus. Among these, Type I, III and V collagen genes had higher expression in resistant animals than in susceptible ones, and keratin genes were more suppressed after challenge in susceptible animals than in resistant ones. These results suggest that some of the genetic variation for tick resistance may be explained by genes related to skin structure.

### Host Resistance to Tick-borne Diseases

Tick-borne diseases are a more complex problem than ticks themselves. There are a number of different pathogens that may be transmitted by each tick species, and the incidence of tick-borne diseases is dependent on seasonal and geographical distribution of the vector. As with most vector-dependent diseases, outbreaks are expected after long periods of low exposure to the vector or introduction of an infected vector to a vector-free area.

In bovine species, the most relevant pathogens are Babesia bovis, Babesia bigemina and Anaplasma marginale, transmitted by R. microplus; Babesia

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**Table 14.2.** QTL for tick resistance identified on Holstein × Gyr F₂ population.

<table>
<thead>
<tr>
<th>Season</th>
<th>Chromosome</th>
<th>P</th>
<th>Position (cM)</th>
<th>D</th>
<th>% Variance explained</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dry</td>
<td>7</td>
<td>0.01</td>
<td>73</td>
<td>Yes</td>
<td>1.90</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>0.01</td>
<td>18</td>
<td>No</td>
<td>6.20</td>
</tr>
<tr>
<td></td>
<td>14</td>
<td>0.05</td>
<td>25</td>
<td>Yes</td>
<td>3.20</td>
</tr>
<tr>
<td></td>
<td>15</td>
<td>0.01</td>
<td>60</td>
<td>No</td>
<td>2.26</td>
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<tr>
<td></td>
<td>27</td>
<td>0.05</td>
<td>5</td>
<td>No</td>
<td>4.80</td>
</tr>
<tr>
<td>Rainy</td>
<td>4</td>
<td>0.05</td>
<td>98</td>
<td>Yes</td>
<td>2.4</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>0.05</td>
<td>132</td>
<td>Yes</td>
<td>1.70</td>
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<tr>
<td></td>
<td>11</td>
<td>0.05</td>
<td>32</td>
<td>No</td>
<td>3.4</td>
</tr>
<tr>
<td></td>
<td>18</td>
<td>0.01</td>
<td>60</td>
<td>Yes</td>
<td>1.97</td>
</tr>
<tr>
<td></td>
<td>23</td>
<td>0.05</td>
<td>50</td>
<td>No</td>
<td>3.6</td>
</tr>
</tbody>
</table>

Defined as: Season in which ticks were counted; F statistics’ P value; dominance deviation; proportion of the phenotypic variance explained by the QTL; this QTL was not tested for dry season data.
Ticks and Tick-Borne Diseases in Cattle

...divergens, transmitted by *Ixodes ricinus*; *Theileria annulata*, transmitted by ticks from the genus *Hyalomma*; and *Theileria parva*, transmitted by *Rhipicephalus appendiculatus*, *Rhipicephalus zambeziensis* and *Rhipicephalus duttoni* (Table 14.3). Given the variety of tick-borne pathogens, resistance will be considered for each pathogen separately.

### Table 14.3. Tick-borne pathogens that affect cattle. (From De La Fuente *et al.*, 2008; Maillard *et al.*, 2003; Shkap *et al.*, 2007.)

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Major vector</th>
<th>Disease</th>
<th>Known geographic distribution</th>
<th>Host</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Babesia bigemina</em></td>
<td><em>Rhipicephalus</em> spp.</td>
<td>Cattle babesiosis</td>
<td>Africa, America, Asia, Australia</td>
<td>Cattle, buffalo</td>
</tr>
<tr>
<td><em>Babesia bovis</em></td>
<td><em>Rhipicephalus</em> spp.</td>
<td>Cattle babesiosis</td>
<td>Africa, America, Asia, Australia</td>
<td>Cattle, buffalo</td>
</tr>
<tr>
<td><em>Babesia major</em></td>
<td><em>Haemaphysalis</em> spp.</td>
<td>Cattle babesiosis</td>
<td>Europe</td>
<td>Cattle</td>
</tr>
<tr>
<td><em>Babesia divergens</em></td>
<td><em>Ixodes</em> spp.</td>
<td>Cattle babesiosis</td>
<td>North-west Europe, Spain, UK, Ireland, Tunisia</td>
<td>Cattle, human</td>
</tr>
<tr>
<td><em>Theileria annulata</em></td>
<td><em>Hyalomma</em> spp.</td>
<td>Tropical theileriosis</td>
<td>Eurasia, Africa, Central Asia</td>
<td>Cattle, camel</td>
</tr>
<tr>
<td><em>Theileria parva</em></td>
<td><em>Rhipicephalus appendiculatus</em></td>
<td>East Coast Fever disease</td>
<td>Africa</td>
<td>Cattle</td>
</tr>
<tr>
<td><em>Theileria lawrencei</em></td>
<td><em>Rhipicephalus zambeziensis</em></td>
<td>Corridor disease</td>
<td>Africa</td>
<td>Cattle</td>
</tr>
<tr>
<td><em>Theileria mutans</em></td>
<td><em>Amblyomma hbraeum</em>, A. lepidum, A. variegatum, A. cohaerens, A. Gemma</td>
<td>Benign theileriosis</td>
<td>Africa</td>
<td>Cattle</td>
</tr>
<tr>
<td><em>Theileria taurotragi</em></td>
<td><em>R. appendiculatus</em>, Rhipicephalus pulchellus, R. zambeziensis</td>
<td>Benign theileriosis</td>
<td>Africa</td>
<td>Cattle</td>
</tr>
<tr>
<td><em>Ehrlichia ruminantium</em></td>
<td><em>Amblyomma</em> spp.</td>
<td>Heartwater</td>
<td>Sub-Saharan Africa Carribean Islands</td>
<td>Cattle, sheep, goats</td>
</tr>
<tr>
<td><em>Dermatophilus congoensis</em></td>
<td>A. variegatum</td>
<td>Dermatophilosis</td>
<td></td>
<td>Cattle</td>
</tr>
<tr>
<td><em>Anaplasma marginale</em>, <em>Anaplasma centrale</em></td>
<td>Various (arthropod, mechanical, e.g. needles)</td>
<td>Anaplasmosis</td>
<td>Worldwide</td>
<td>Cattle</td>
</tr>
</tbody>
</table>
Immunological responses to tick-borne diseases

Cattle infected with *B. bovis* develop fever, depression and haemoglobinuria, often accompanied by anaemia and abortion. Neurological signs are frequently observed and a fatal cerebral disease, associated with the adherence of infected erythrocytes to brain microcapillary endothelial cells, may also occur. Infection with *B. bigemina* is usually less severe, with less pronounced fever and sporadic neurological signs (Jonsson *et al*., 2008; Brown, 2001).

Immunity to the genus *Babesia* is documented in several mammalian species and efforts to understand protective mechanisms and immune-dominant proteins have been made in order to develop vaccines. A peculiarity of *Babesia* parasites is that they replicate exclusively within the erythrocytes, which is devoid of molecules from the MHC.

Protection against *Babesia* infection involves both innate and acquired immunity. In naive animals infected with virulent *B. bovis* parasites, resolution of acute infection results from the innate immune response (Brown, 2001). This response depends on activation of macrophages via interferon gamma (IFN-γ) and parasite-derived products, such as deoxyribonucleic acid (DNA), followed by production of toxic macrophage metabolites, including nitric oxide (NO). The spleen is the clearance site for *B. bovis*-infected erythrocytes, with splenectomized animals developing clinical disease earlier than non-splenectomized ones (Zintl *et al*., 2005; Brown *et al*., 2006). This spleen-dependent innate response seems to be more effective in young than in adult bovines, which could be related to faster activation of IL-12 and IFN-γ-mediated NO production in spleen cells (Goff *et al*., 2001).

Regulation of innate immunity is crucial. Some immune mediators produced by cells of the innate immune system that are protective against intracellular pathogens, such as IFN-γ, type I IFN, NO and tumour necrosis factor alpha (TNF-α), are also implicated in the severe pathogenesis associated with infection by *B. bovis* and *Theileria* spp. parasites (Brown, 2001; Brown *et al*., 2006).

Acquired immunity to *Babesia* spp. may be developed after immunization or persistent infection. The protective role of antibodies is demonstrated by passive protection obtained *in vivo* by immune serum administration. However, there is no evidence of the effect of immune serum on parasite viability *in vitro*, suggesting that these antibodies act as opsonins for activated macrophages, instead of as neutralizing antibodies (Brown, 2001).

Recovery from acute infection with *B. bigemina* or *B. bovis* does not result in cure. Instead, recovered animals remain persistently infected and do not develop clinical disease upon reinfection with the same strain. These healthy recovered animals act as reservoirs for the maintenance of vector infection rates. In tropical areas, vector and reservoir availability throughout the year guarantees exposure of young animals to *Babesia* spp. before the passive immunity acquired through colostrum is lost, i.e. when calves are approximately 2 months old. This equilibrium between exposure and immune response results in an endemic stability. If this equilibrium is broken by long periods of low exposure to the infected vector, clinical disease may occur (Oliveira *et al*., 2008).
However, based on serological evidence in Australia, it was reported that the endemic stability is uncommon with respect to the three tick fever organisms, *B. bovis*, *B. bigemina* and *A. marginale* (Serugga et al., 2003).

Theileriosis is a severe disease of cattle and domestic buffaloes caused by protozoan of the genus *Theileria*. *T. parva*, causing East Coast fever (ECF), is essentially present in central and eastern Africa. *T. annulata*, causing tropical theileriosis or Mediterranean Coast fever (MCF), is present in northern Africa, southern Europe, the Middle East and central Asia. Both diseases are characterized by lymph node augmentation, high fever, anorexia, nasal and ocular discharge and diarrhoea. Death occurs after 7–10 days in 90% of cases.

As with most members of the phylum *Apicomplexa*, *Theileria* infect nucleated cells, macrophages and lymphocytes, before developing to a merozoite stage in the erythrocytes. During this period of infection, they hide within these cells and modulate host gene expression to allow parasite replication.

Macrophages infected by *T. annulata* are up-regulated for pro-inflammatory cytokines, IL-1β, IL-6, TNF-α and BoLA class II genes, and down-regulated for surface proteins, most of which are involved in cell signalling. Some of the clinical signs of the disease may be related to the parasite-induced cytokine profile, since they are similar to administration of IL-6 and TNF-α. A detailed review on theileriosis-related gene expression profiles is found in Glass and Jensen (2007).

Parasite dose and virulence are determinants of disease severity, which may go from acute lethal to clinical recovery. In the latter, persistent and solid immunity is achieved (Preston et al., 1999).

**Genetic variation for resistance to tick-borne diseases in cattle**

Host resistance to diseases transmitted by ticks is not as well documented in cattle as is resistance to ticks themselves. In general, *B. indicus* cattle are more resistant to tick-borne diseases, although this resistance does not apply to *A. marginale* (Bock et al., 1997, 1999).

In the case of *Babesia* spp., infection rates are affected by age, climate, soil and host genetics. While the *B. indicus* Nelore breed is considered resistant to *B. bigemina*, the frequency of infection in this breed is similar to cross-bred and *B. taurus* animals (Oliveira et al., 2008). So the main difference among resistant and susceptible breeds is not related to whether they become infected but, rather, to how they overcome babesiosis, i.e. resilience. By comparing ticks collected from pure Nelore and cross-breds, Oliveira et al. (2008) demonstrated that there is no difference in tick infestation rate among genetic groups. The practical implication of this finding is that introduction of *B. indicus* would not result in clearing the vector, i.e. reduce infection levels, and would not break endemic stability.

Within-breed individual variability occurs for babesiosis (Bock et al., 1999), but no heritability estimate is available, since measuring resistance in a large number of individuals is not possible. Three categories of resistance were
reported by Benavides and Sacco (2007) upon challenge of pure *B. taurus* naive heifers with *B. bovis*: susceptible, intermediate and resistant. The susceptible category represented 45% of the assayed animals (120 Hereford and 120 Aberdeen Angus) and was characterized by animals that had to be medicated to avoid death. The second and third categories overcame infection without treatment. Animals classified as intermediate, 27% of those challenged, had moderate reduction of packed cell volume, without clear manifestation of clinical signs. Resistant animals, the remaining 28%, had less of a packed cell volume reduction with only minor increase in body temperature. This is the only report of variation in resilience to *Babesia* in *B. taurus*. Mechanisms underlying haemoparasite resistance are not clear, but they may be related to both impairment of parasite replication and mechanisms of anaemia control (Naessens, 2006).

Genetic variation is also reported for resistance to theileriosis. The mortality rate from ECF can be up to 100% in cattle from non-endemic areas, but is usually low in indigenous zebu cattle from endemic areas. The Sahiwal (Glass *et al*., 2005) and Kenana zebu breeds are considered resistant to tropical theileriosis (*T. annulata*), as are some taurine breeds that emerged within endemic areas.

**Genes and Markers for Resistance to Tick-borne Diseases**

No relevant information on markers or candidate genes associated with bovine resistance to babesiosis is found in the literature, but clues on the genetic control of variation in *Babesia* resistance may come from model species. In mice, a locus linked to resistance to babesiosis was mapped near the telomeric region of mice Chr 16, using a C57BL/6 (resistant) C3H/HeJ (susceptible) backcross and recombinant inbred strains (Aguilar-Delfin *et al*., 2003).

Some pathways and candidate genes for resistance to *Theileria* are emerging from comparisons of immune profiles of resistant and susceptible animals. Glass *et al*. (2005) compared responses to experimental infection with *T. annulata* in Sahiwal and Holstein calves. All Sahiwal calves survived without treatment and with few clinical alterations, accompanied by significantly less response in acute-phase proteins, \( \alpha_1 \) acid glycoprotein and haptoglobin, than for the Holsteins. Additionally, the Sahiwals had lower resting levels of \( \alpha_1 \) acid glycoprotein than the Holsteins \( (P < 0.05) \). Production of a third acute-phase protein, serum amyloid A, had very similar kinetics in both breeds. Production of acute-phase proteins is stimulated by cytokine pathways that might also be involved in pyrexic, cachectic and anorexic signs in tropical theileriosis. From these results it is possible to postulate that the ability to avoid overstimulation of specific cytokine pathways could help in host recovery from infection.

Using the same rationale of comparing Sahiwal and Holstein, but aiming at global transcription patterns through the use of microarrays, Glass and Jensen (2007) demonstrated that a variety of cellular pathways are altered upon *in vitro* infection of monocytes with *T. annulata*. These pathways include
toll-like receptor and mitogen-activated protein kinase. Among the differentially expressed genes between breeds, about two-thirds were differentially expressed also in resting (non-infected) cells, showing that fundamental breed differences could account for the way they respond to infection. Further exploration of these microarray data, classifying genes according to the most common biological processes in Gene Ontology, revealed differential expression of genes encoding proteins expressed in the plasma membrane or intracellular space or related to cell adhesion (Jensen et al., 2008).

Although there is little development on markers for tick-borne diseases in livestock, one of the most relevant results on the use of marker-assisted selection for resistance is the work by Maillard et al. (2003), in dermatophilosis, a severe skin disease caused by the filamentous actinomycete bacterium *Dermatophilus congoensis* in which disease severity is related to the immune modulation exerted by the tick *Amblyomma variegatum*. Eugenic selection against the BoLA-DRB3.2'09/*45 and DQB'1804 alleles, strongly associated to susceptibility to dermatophilosis, was applied to a Brahman breeding programme in Martinique. The disease incidence was reduced from 0.76 to 0.02 in 5 years of marker-assisted selection.

**Conclusions**

In a study on assessing the vulnerability of the Australian beef industry to impacts of the cattle tick under a climate change scenario, White et al. (2003) predicted significant expansions in potential geographical impacts, with increased abundance of tick populations and reductions in cattle productivity. With global warming being perceived as a certainty, its cascading effect on various facets of cattle farming, including the increased challenge of parasitic infestations such as ticks, needs to be addressed with a holistic approach.

There have been various attempts at controlling ticks and tick-borne diseases in tropical livestock. Breeding for genetic resistance is one of the promising ways to control ticks, although the same cannot be stated for tick-borne diseases as these still need more investigation to characterize the genetic variation and to depict underlying genes and markers. On the other hand, the application of marker-assisted selection would be of greater benefit in the latter case, since conventional breeding for tick-borne diseases, i.e. scoring phenotypes for resistance in a large number of animals, is almost impractical in commercial breeding schemes.

Efforts are currently continuing with large projects in Australia (e.g. projects under the Cooperative Research Centre for Beef Genetic Technologies) and Brazil (e.g. research initiatives from Embrapa, with support from the Brazilian National Research Council (CNPq)) aiming to develop genetic markers for tick resistance and to develop tick vaccines. While these efforts will eventually lead to identification of genes or genetic markers underpinning the variation in tick resistance, future research should aim to effectively use this knowledge in breeding programmes to improve tick resistance without compromising the genetic gains accrued over generations in other economic traits.
Acknowledgements

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Author Queries:

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