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A ten-year review of commercial vaccine performance for control of tick infestations on cattle

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Abstract

Ticks are important ectoparasites of domestic and wild animals, and tick infestations economically impact cattle production worldwide. Control of cattle tick infestations has been primarily by application of acaricides which has resulted in selection of resistant ticks and environmental pollution. Herein we discuss data from tick vaccine application in Australia, Cuba, Mexico and other Latin American countries. 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. Commercial tick vaccines reduced tick infestations on cattle and the intensity of acaricide usage, as well as increasing animal production and reducing transmission of some tick-borne pathogens. Although commercialization of tick vaccines has been difficult owing to previous constraints of antigen discovery, the expense of testing vaccines in cattle, and company restructuring, the success of these vaccines over the past decade has clearly demonstrated their potential as an improved method of tick control for cattle. Development of improved vaccines in the future will be greatly enhanced by new and efficient molecular technologies for antigen discovery and the urgent need for a tick control method to reduce or replace the use of acaricides, especially in regions where extensive tick resistance has occurred.

Keywords: Tick, Vaccine, Bm86, Gavac, TickGard, Boophilus

Introduction

Ticks parasitize terrestrial vertebrates and transmit pathogens that affect animal and human populations (Estrada-Peña and Jongejan, 1999; Parola and Raoult, 2001; Barker and Murrell, 2004). Tick infestations especially impact cattle production worldwide. For example, *Boophilus* spp. are major tick pests of cattle in tropical and subtropical regions of the world. Infestations with the cattle tick, *Boophilus microplus*, economically impact cattle production by reducing weight gain and milk production, and by transmitting pathogens that cause babesiosis (*Babesia bovis* and *Babesia bigemina*) and anaplasmosis (*Anaplasma marginale*) (Peter *et al.*, 2005).

Control of tick infestations has been difficult because ticks have few natural enemies. Integrated tick

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management strategies include the adaptation of different control methods to a geographic area. A major component of integrated tick control methods is the application of acaricides. However, use of acaricides has had limited efficacy in reducing tick infestations and is often accompanied by serious drawbacks, including the selection of acaricide-resistant ticks, environmental contamination and contamination of milk and meat products with drug residues (Graf *et al.*, 2004). Furthermore, development of new acaricides is a long and expensive process. All of these issues reinforce the need for alternative approaches to control tick infestations (Graf *et al.*, 2004). Other approaches proposed for tick control have included the use of hosts with natural resistance to ticks, pheromone-impregnated decoys for attracting and killing ticks, biological control agents and vaccines (de la Fuente and Kocan, 2006; Sonenshine *et al.*, 2006; Willadsen, 2006).

The feasibility of controlling tick infestations through immunization of hosts with selected tick antigens was demonstrated by Allen and Humphreys (1979). Control of ticks by vaccination has the advantages of being cost-effective, reducing environmental contamination and preventing the selection of drug-resistant ticks that result from repeated acaricide application. In addition, development of vaccines against ticks using multiple antigens that could target a broad range of tick species may also prevent or reduce transmission of pathogens (de la Fuente and Kocan, 2006; de la Fuente *et al.*, 2006a, b; Willadsen, 2006; Nuttall *et al.*, 2006).

In the early 1990s, vaccines were developed that induced immunological protection of vertebrate hosts against tick infestations. These vaccines contained the recombinant *B. microplus* Bm86 gut antigen (Willadsen *et al.*, 1989; Rand *et al.*, 1989; Rodríguez *et al.*, 1994; recently reviewed by Willadsen, 2004, 2006; de la Fuente and Kocan, 2003, 2006). Two vaccines using recombinant Bm86 were subsequently registered in Latin American countries (Gavac) and Australia (TickGARD) during 1993–1997 (Cobon *et al.*, 1995; de la Fuente *et al.*, 1995; Massard *et al.*, 1995; Vanegas *et al.*, 1995; Willadsen *et al.*, 1995; Canales *et al.*, 1997). These vaccines reduce the number of engorging female ticks, their weight and reproductive capacity. Thus the greatest vaccine effect was the reduction of larval infestations in subsequent generations. Controlled field trials using Bm86-based vaccines conducted in Cuba, Mexico, Brazil, Colombia and Australia demonstrated successful control of *B. microplus* and *Boophilus annulatus* infestations (Cobon *et al.*, 1995; Rodríguez *et al.*, 1995a, b; Willadsen *et al.*, 1995; Canales *et al.*, 1997; de la Fuente *et al.*, 1998, 1999; Redondo *et al.*, 1999; Jonsson *et al.*, 2000a). A correlation between antibody responses of cattle immunized with the Bm86 vaccine and tick fertility was demonstrated in Australia (Cobon *et al.*, 1995) and Cuba (de la Fuente *et al.*, 1998). Strategic integrated acaricide application and vaccination in relation to seasonal tick populations was proposed as a more cost-effective and environmentally sound means of controlling tick infestations (Lodos *et al.*, 1999, 2000). Controlled field trials in combination with acaricide treatments demonstrated that an integrated approach resulted in control of tick infestations while reducing the use of acaricides (de la Fuente *et al.*, 1998; reviewed by de la Fuente and Kocan, 2003).

While a number of difficulties were experienced in the commercialization of tick vaccines, the use of Bm86 vaccines for the control of tick infestations has continued for a decade after their registration and commercialization. The results of commercial field application of tick vaccines have been reported only briefly. These results, reviewed herein with updated information, demonstrate the importance of vaccines for the control of tick infestations. Analysis of reasons for vaccine successes and failures provides important information towards planning the development of improved cattle tick vaccines in the future.

The Cuban experience

The recombinant Bm86 tick vaccine (Gavac) was developed by the Center for Genetic Engineering and Biotechnology (Havana, Cuba) and released by Heber Biotec S.A. (Havana, Cuba) in 1993. The first study of commercial field use of this tick vaccine in Cuba was a retrospective analysis of the cost-effectiveness of vaccination using data from 260,587 cattle (de la Fuente *et al.*, 1998). The results of this study demonstrated the effectiveness of Bm86 vaccination for the control of *B. microplus* infestations while reducing the number of acaricide treatments needed to maintain tick control by two-thirds. Use of Gavac also resulted in a reduction in the incidence of anaplasmosis and babesiosis with over $6 million in savings for the cattle industry (de la Fuente *et al.*, 1998).

Recently, the analysis of results of the field use of Gavac in Cuba was extended to include 588,573 dairy cattle (Rodríguez Valle *et al.*, 2004). Over a period of 8 years (1995–2003), the number of acaricide treatments for tick control were reduced by 87% with an overall reduction of 82% in the consumption of acaricides for tick control in the country. Over a 6-year period, the use of Gavac also lowered the incidence and mortality of cattle due to babesiosis from 54 clinical cases and six fatal cases to 1.9 clinical cases and 0.18 fatal cases per 1000 cattle (Rodríguez Valle *et al.*, 2004).

These results demonstrated that the implementation of integrated tick control programs using the combination of the tick vaccine and strategic acaricide treatments resulted in a more cost-effective tick control program in Cuba. However, Cuban conditions are unique with respect to tick control programs because the centralized socialist state economy controls cattle production and insures implementation of tick control programs. State-sponsored use of the tick vaccine for the control of tick

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infestations in cattle has continued since 1995, providing an exceptional opportunity for evaluation of tick vaccine field performance.

The Australian experience

The tick vaccine TickGard, developed by the Commonwealth Scientific and Industrial Research Organisation (CSIRO) in collaboration with Biotech Australia Pty. Ltd., was released by Hoechst Animal Health in Australia in 1994. As a novel product with a mode of action quite different from that of the acaricides then available, registration requirements were demanding and detailed. Approximately 18,000 cattle were vaccinated in trials prior to commercial release. Many of the later trials were also used to test producer willingness and ability to apply a protocol that required prophylactic use of a vaccine to suppress tick populations, together with reduced acaricide application, if necessary, to cope with periods of peak tick infestation. The feedback was positive. Reduction in acaricide use, as compared with pre-vaccine historical practice, became a *de facto* measure of vaccine efficacy.

In the first four years following its release, sales of the vaccine grew rapidly and TickGard became the highest value tick treatment sold in the country. However, towards the end of the decade, a number of commercial factors came into play. These included the breakup of Hoechst AG, a major part of which is now part of Aventis (Strasbourg, France), the separation of Hoechst Animal Health as an independent company, the closure of Biotech Australia Pty. Ltd., the company manufacturing the vaccine and the eventual sale of Hoechst Animal Health to Intervet International (Boxmeer, The Netherlands). As a result of these company restructurings, the vaccine disappeared from the market. After several years the vaccine was re-introduced to the market by Intervet Australia Pty. Ltd. (Bendigo, Australia), apparently being targeted at the very small northern Australian dairy industry rather than the vastly larger beef industry. After a short period, the product ceased to be sold by Intervet and is now available only through a producer organization.

The information available on the results of field use of TickGuard in Australia is scarce (Cobon *et al*., 1995; Willadsen *et al*., 1995; Jonsson *et al*., 2000a). The results of the commercial field application of TickGuard in Australia were first reported by Cobon *et al*. (1995). During the first year of commercialization in Australia when the vaccine was used in over 300 dairy and beef cattle farms, control of cattle tick populations was obtained, accompanied by a significant reduction in acaricide usage. In on-farm trials in 1996–1997 on 26 beef cattle farms, a single booster vaccination reduced the average number of acaricide treatments by 2.4, while a quarter of the cattle farms found that acaricide application was not required after vaccination. Therefore, the combination of vaccine and acaricide, even though more complex than traditional practices, was acceptable to 90% of the farmers surveyed (Cobon, personal communication). Later, Jonsson *et al*. (2000a) reported that vaccination of a dairy herd against the cattle tick resulted in a 56% reduction in tick numbers in the field in a single generation, a 72% reduction in tick reproductive performance and an increase in cattle live weight gain of 18.6 kg over a 6 month period. Anecdotal evidence is that farms using the vaccine for a sustained period observed a very substantial reduction in the need for acaricide, to low or zero levels. These results, although obtained with a limited number of animals, support the efficacy of tick vaccines for the control of cattle tick infestations under Australian conditions.

The results in Mexico

The Gavac vaccine was released in Mexico in 1997 by Revetmex S.A. de C.V. (Mexico City, Mexico). Controlled pen and field trials in Mexico provided evidence of the effect of recombinant Bm86 vaccination for the control of *B. microplus* and *B. annulatus* infestations (Fragoso *et al*., 1998; de la Fuente *et al*., 1999; Redondo *et al*., 1999). Nevertheless, the tick vaccine had a limited use in Mexico due to difficulties associated with its commercialization and the lack of efficacy of Bm86 vaccination against *Amblyomma cajennense*, a tick that occurs concurrently with *Boophilus* spp. in some regions. However, despite these difficulties, tick vaccines have been an important tool for integrated control of tick infestations in Mexico due to the major growing problem of tick resistance to acaricides (Foil *et al*., 2004; Rodriguez-Vivas *et al*., 2006a, b).

In a recent trip to Mexico, we (CA and JF) visited the ranch Tixtla in the municipality of Soto la Marina, Tamaulipas. Vaccination of cattle against ticks with Gavac (Revetmex, Mexico City, Mexico) began on this ranch in 1997 and has continued to the present. This ranch has 2600 crossbred cattle on approximately 2500 ha. Before use of the vaccine in 1997, 24 acaricide treatments were used per year for control of cattle tick infestations that reached over 100 adult ticks per animal. In the last two years, only 7–8 acaricide treatments have been required per year and tick infestations have been maintained at levels lower than 20 ticks per animal. These results represented a 67% reduction in acaricide usage for control of cattle tick infestations. These results are similar to those obtained in other ranches in this region using Gavac for the control of tick infestations.

Although limited, vaccination for tick control has been used in Mexico for a decade since the introduction of the vaccine in the market in 1997. Today, an increasing demand for the vaccine is driven by the selection of acaricide-resistant ticks. As a result of this demand, the state of Tamaulipas is sponsoring the use of the tick vaccine, providing financial assistance to cattle producers through governmental programs.

Preliminary results in South American countries

The Gavac tick vaccine was registered and commercialized in Colombia and Brazil in 1994 and 1995, respectively. During the first year, the vaccine was adopted in Colombia and used in over 100 dairy, beef and dairy–beef dual-purpose cattle farms (Vanegas *et al.*, 1995). Despite differences between cattle production systems, reduction of acaricide treatments after vaccination averaged 57%. Use of Gavac also reduced the incidence of anaplasmosis (Vanegas *et al.*, 1995). One year after vaccination, the number of acaricide treatments was reduced in crossbred cattle farms in Doima and Santa Cruz, Ibagué, by 72 and 77%, respectively (de la Fuente and Kocan, 2003).

Over 1000 cattle were vaccinated with Gavac after its commercial release in Brazil in 1995 (Massard *et al.*, 1995). Preliminary results of field vaccine usage documented an average reduction of 50% in acaricide treatments for cattle tick control, including farms with different production conditions and cattle breeds. Regrettably, problems with commercialization have limited the use of Gavac in these countries, thus limiting the information on the long-term effect of the vaccine in the field.

Summary and conclusions

Tick vaccines containing recombinant Bm86 antigen preparations were registered in several Latin American countries and Australia during 1993–1997. Use of these commercial vaccines in the field has been reported in Cuba, Australia, Mexico, Colombia and Brazil. Ten years later, commercial tick vaccine usage remains documented in Cuba (Rodríguez Valle *et al.*, 2004; Gavac, sold by Heber Biotec S.A., Havana, Cuba: http://www.heber-biotec.com/Veterinarios.asp), Mexico (results reported above; Gavac, sold by Revetmex S.A. de C.V., Mexico City, Mexico: http://www.revetmex.com/rev_esp/cat/cat_07/cat_0707.html) and Australia (Queensland Government, 2006; TickGARD, currently sold by the Queensland Dairy Farmers Organization under an agreement with Intervet Australia Pty. Ltd., Bendigo, Australia: http://www.abc.net.au/rural/qld/stories/s1084200.htm).

However, existing tick vaccines have had relatively small impact on tick control efforts. As discussed previously (Willadsen, 2006), a combination of commercial and technical problems has contributed to the lack of vaccine usage. Among these problems the most important are: (a) the inefficacy of Bm86-based vaccines against some tick species (de la Fuente *et al.*, 2000; de Vos *et al.*, 2001), (b) the lack of the knock-down effect exhibited by chemical acaricides, (c) difficulties in the commercialization of tick vaccines due to its new concept for tick control and the competition with marketing efforts towards selling and use of acaricides, (d) the lack of interest by commercial companies, (e) company restructuring and (f) incorrect use of tick vaccines in some countries due to insufficient information about vaccine properties and the lack of integrated tick control strategies in some countries.

Commercial constraints are important. For example, there is experimental evidence that inclusion of a second recombinant antigen in the existing vaccine could double efficacy (Willadsen *et al.*, 1996) with potentially a very useful impact in the field. Given the costs of re-registration of the vaccine however, the improvement was judged not to be commercially attractive.

Nevertheless, successes in the commercial use of tick vaccines in the field, as discussed herein, provide evidence of the potential positive impacts of tick vaccines for cattle. Tick vaccines were most successfully used in state-sponsored integrated tick control programs that facilitated proper vaccine use and implementation. Furthermore, in some cases, these programs absorbed part of the costs associated with the vaccine, therefore reducing expenses for cattle producers, as well as boosting the vaccine market.

In summary, tick vaccines have been shown to be a cost-effective and environmentally sound approach to tick control. When commercial tick vaccines were used in the field, effective control of cattle tick populations resulted, accompanied by improved cattle production and reduced dependence on acaricides. The long-term benefits of reduced acaricide usage are considerable, including environmental and health considerations as discussed herein. In addition, a study of acaricide resistance and management practice in Australia clearly demonstrated that the frequency of acaricide tick resistance correlated directly with the frequency of treatments (Jonsson *et al.*, 2000b). By decreasing the rate of selection of acaricide-resistant ticks, the useful life of an acaricide will be prolonged providing a control option until more effective tick vaccines are developed.

Together, these results support the importance of tick vaccines in integrated control strategies, both in regions where acaricide-resistant ticks have or may become a major problem for the cattle industry. Although the lack of funding and commercial interest may be a limiting factor to development of new vaccines, the information accumulated after ten years of tick vaccine use in the field supports continuation of research programs to develop more effective tick vaccines. Development of improved vaccines in the future will be greatly enhanced by molecular technologies and systems biology approaches that are contributing to the discovery of new candidate vaccine antigens. The urgent need for an effective tick control method to reduce or replace the use of acaricides is notable in regions where extensive tick resistance has occurred.

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