

# **Vaccination against Ticks and the Control of Tick-Borne Disease**

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# Ticks and Tick Borne Disease: Why Recombinant Vaccines?

Today, a mixture of resistant genotypes and chemical pesticides are the main weapons against ticks. Neither is completely satisfactory. Poor animal productivity is the result.

## Advantages of vaccines:

- **Stable, transportable and safe**
- **Applicable to all genotypes**
- **Potentially cheap**
- **Non-contaminating**
- **Tolerant of poor application**

## Disadvantages:

- **Do they work?**
- **Highly specific to target organism(s)**

# Vaccines: the Critical Questions

How good does a vaccine need to be ?

Is the effect on livestock production due to the ticks directly, or through the transmission of disease?

Is it scientifically feasible to make a vaccine ?

Does a vaccine work at all ?

Can a vaccine protect against multiple species ?

Can the efficacy of existing vaccines be improved ?

What role do tick vaccines have in the control of tick borne disease ?

Is there a realistic way to manufacture, register, market and distribute a vaccine ?

## *Boophilus microplus*: the problem

*B. microplus* causes production losses in beef and dairy cattle in northern Australia, from Mexico to Uruguay and Argentina, in China, south east Asia and significant parts of Africa.

Its impact comes through blood loss and “tick worry” as well as through the transmission of *Babesia bovis*, *Babesia bigemina* and *Anaplasma marginale*.

It is controlled in Australia, as elsewhere in the world, through a combination of tick resistant cattle and pesticides.

Problems of pesticide resistance, chemical residues in food and the environment and the unsuitability of tick resistant cattle for all production systems make the current situation unsatisfactory. In addition, acquired resistance to ticks is, in almost all circumstances, insufficient to prevent production loss and does not prevent transmission of disease and other parasites.



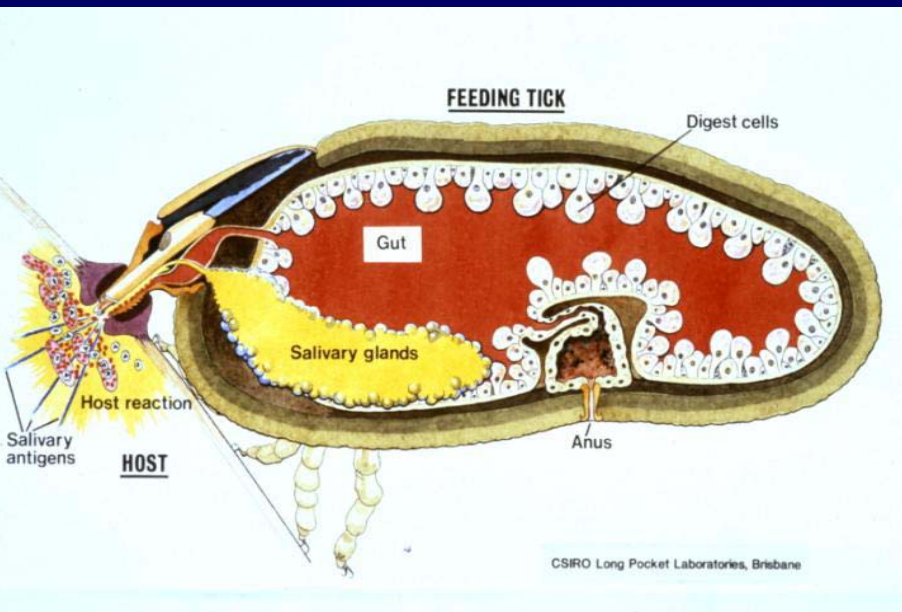


## Vaccination against *B. microplus*

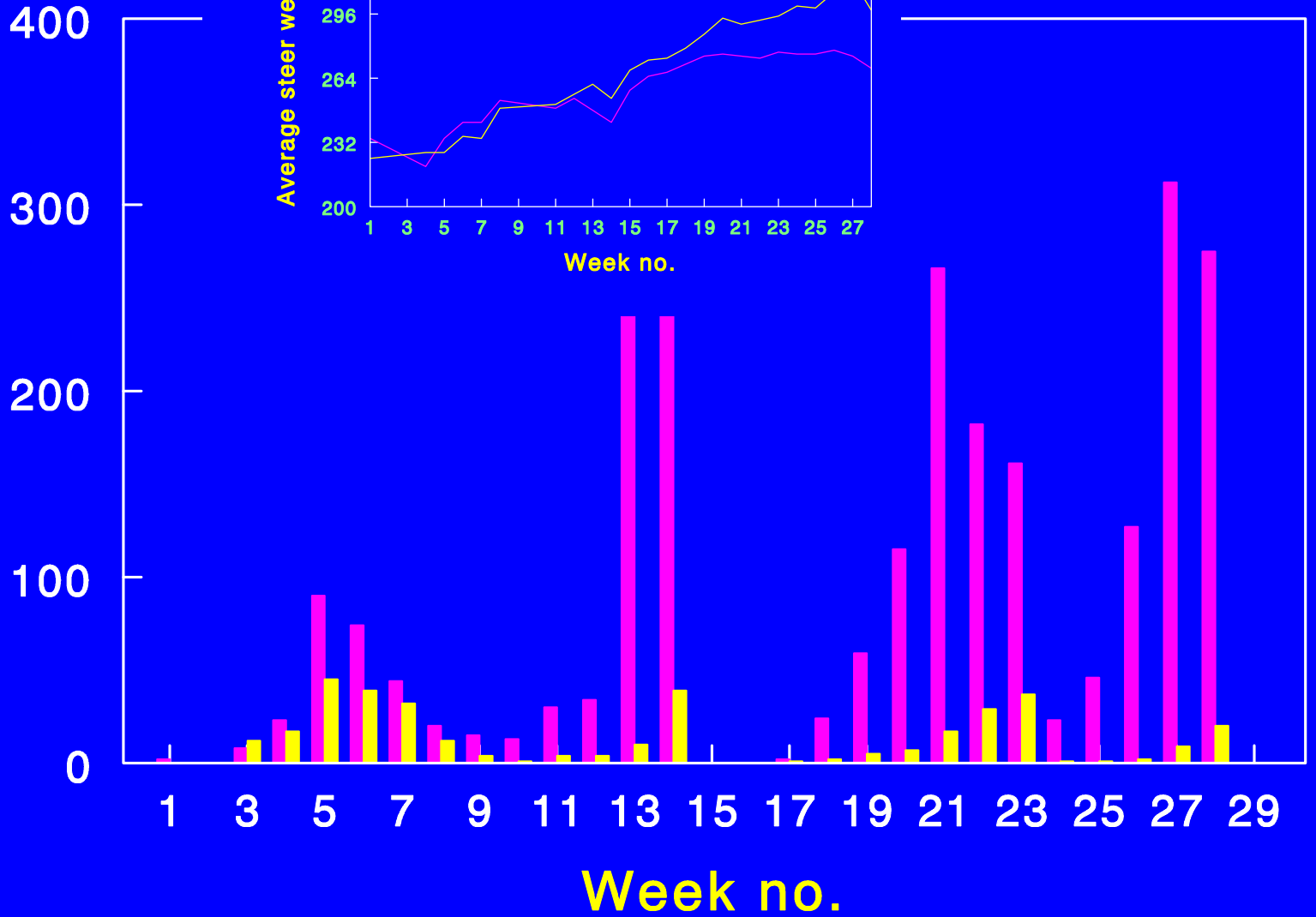
Vaccination with crude tick material could be highly efficacious

The mechanism was via attack on the tick's gut cells

An antigen was identified from the surface of those cells which was effective in low microgram amounts



Mean side counts for group



# Feasibility of Vaccinating against Ticks

After more than 12 years of research and field trials with 18,000 cattle, a vaccine was released commercially in Australia in 1994

Two commercial vaccines are available for *Boophilus microplus*, both based on the Bm86 antigen: TickGARD in Australia and GAVAC in Cuba and parts of South America



## Post-Commercialisation Experience

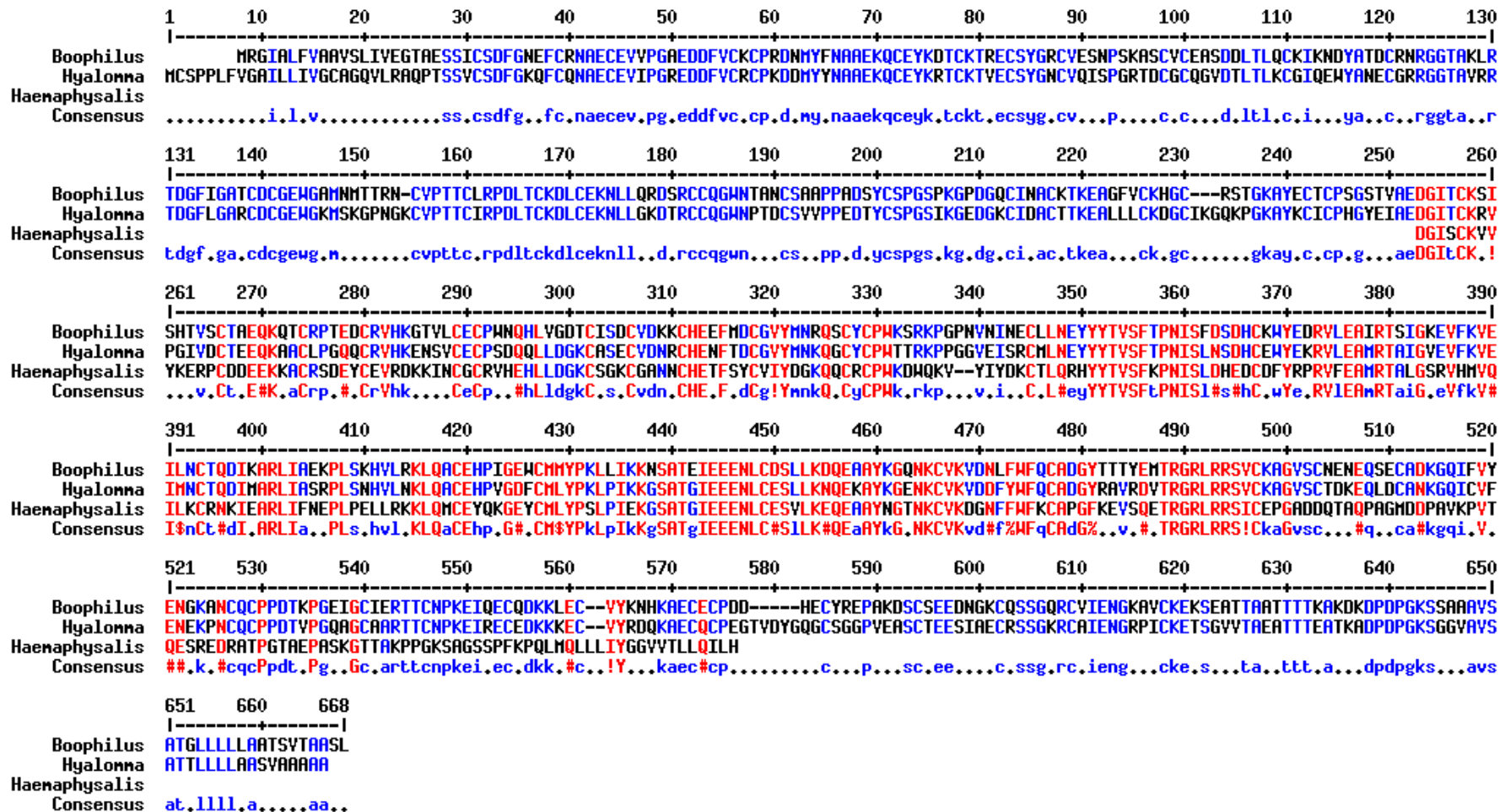
From 1995 to 1997, over 640,000 doses of vaccine were sold in Queensland, despite starting from a zero base with a very novel product. Over half a million cattle have been vaccinated in Cuba.

The vaccine is mostly used in an integrated way with limited pesticide. A significant decrease in pesticide usage is almost always recorded. The integrated approach is acceptable to most farmers. Some farms claim the vaccine on its own gives good tick control, particularly after several years of use. Cuba claims nationally a 10-fold reduction in acaricide consumption.

Isolate variation in sequence occurs as does isolate variation in susceptibility. Nevertheless (with one possible exception) the vaccine may be useful with all strains.

# Can a Tick Vaccine Protect Against Multiple Species ?

## Bm86 alignment: *B. microplus*, *H. longicornis* and *H. anatolicum*



**OTHER TICK SPECIES: SEQUENCE CONSERVATION AND EFFICACY OF VACCINATION WITH  
B. MICROPLUS BM86**

Tick	% Sequence identity	Efficacy	Reference
<i>B. microplus</i> (Y)	100%	89%	Tellam <i>et al.</i> , 1992
<i>B. decoloratus</i>		70%	de Vos <i>et al.</i> , 2001
<i>B. annulatus</i>	97% ( <sup>34</sup> / <sub>35</sub> )	100%	Fragoso <i>et al.</i> , 1998; Pipano <i>et al.</i> , 2003
<i>Haemaphysalis longicornis</i>	48% ( <sup>146</sup> / <sub>301</sub> )		Pickering <i>et al.</i> , unpublished
<i>R. sanguineus</i>	67% ( <sup>488</sup> / <sub>631</sub> )		Pickering <i>et al.</i> , unpublished
<i>R. appendiculatus</i>	78% ( <sup>114</sup> / <sub>147</sub> )	~ zero	de Vos <i>et al.</i> , 2001
<i>H. anatolicum</i>	63% ( <sup>402</sup> / <sub>632</sub> )	High	de Vos <i>et al.</i> , 2001
<i>H. dromedarii</i>		>98%	de Vos <i>et al.</i> , 2001
<i>A. variegatum</i>		0%	de Vos <i>et al.</i> , 2001

Numbers in brackets give the total number of amino acid identities as a fraction of the total number sequenced.

## Can the Current Tick Vaccines be Improved ?

There are two clear options:

Improve the immunological response

This has been done once already with the existing TickGARD vaccine

Improve efficacy through the incorporation of additional antigens

## RECOMBINANT TICK ANTIGENS

Antigen	Tick species	Result	Reference
Bm86	<i>B. microplus</i>	✓	Willadsen <i>et al.</i> , 1995
Bm91 (carboxy dipeptidase)	<i>B. microplus</i>	✓	Willadsen <i>et al.</i> , 1996
5'-Nucleotidase	<i>B. microplus</i>	?	Liyou, 1996
Antigen B	<i>B. microplus</i>	?	Unpublished
Vitellin	<i>B. microplus</i>	x	Tellam <i>et al.</i> , 2002
P29	<i>H. longicornis</i>	✓	Mulenga <i>et al.</i> , 1999
HL34	<i>H. longicornis</i>	✓	Tsuda <i>et al.</i> , 2001
HLS1	<i>H. longicornis</i>	✓	Sugino <i>et al.</i> , 2003
64 TRP	<i>R.</i>	✓	Trimnell <i>et al.</i> , 2002
	<i>appendiculatus</i>		Labuda <i>et al.</i> , 2002
Immunoglobulin binding protein	<i>R.</i>	?	Wang and Nuttall, 1999.
	<i>appendiculatus</i>		

✓ Statistically significant effect demonstrated; ? Effect slight or equivocal; x No demonstrable effect

In addition, at least another 4 well defined, native antigens have been shown to have protective effects

## EXAMPLES OF WELL DEFINED, POTENTIAL TICK ANTIGENS

Antigen	Species	Reference
IL8 binding protein	<i>I. ricinus, D. reticulatus</i>	Hajnicka <i>et al.</i> , 2001
IRIS	<i>I. ricinus</i>	Leboulle <i>et al.</i> , 2002
Da-p36	<i>D. andersoni</i>	Bergman <i>et al.</i> , 2000
Histamine binding protein	Several	Paesen <i>et al.</i> , 2000
MIF (macrophage migration inhibitory factor)	<i>A. americanum</i>	Jaworski <i>et al.</i> , 2001
Immunoglobulin binding proteins	Several	Wang and Nuttall, 1999
Factor Xa inhibitor	<i>O. savignyi</i>	Joubert <i>et al.</i> , 1998

# Tick Vaccines and Tick Borne Disease

## Evidence so far is:

- Reduction in incidence of anaplasmosis and babesiosis in Cuba (but not in all areas) Garcia Garcia *et al.*, 1998
- No transmission of *Babesia bigemina* and reduced effect of *Babesia bovis* transmitted by *Boophilus annulatus* on TickGARD - vaccinated cattle (Pipano *et al.*, 2003)
- Reduced transmission and mortality due to tick borne encephalitis virus in 64 TRP-vaccinated mice (Labuda *et al.*, 2002)

There is tentative evidence that the existing vaccine would be highly efficacious against *Hyalomma spp.* What would be the effect of vaccination on diseases transmitted by *Hyalomma* ticks?

# **Delivery to a Niche Market**

**(and, for ticks and tick borne disease, probably only one market is not a niche market)**

**Four components to vaccine delivery:**

- **Recombinant antigen production: fermentation and post-fermentation processing**
- **Formulation and packaging**
- **Registration and regulatory approval**
- **Distribution (and pricing policy)**

# Manufacture of a Tick ( or Tick-Borne Disease ) Vaccine

It cannot be assumed that a major global animal health or vaccine company will find a vaccine for a tick or tick borne disease commercially attractive.

It is likely alternative routes to market will be necessary.

The production of a recombinant vaccine relies on generic, multi-purpose facilities: fermentation and vaccine formulation plants with multiple uses.

In principle therefore, the manufacture of a recombinant vaccine against a parasitic disease could be organized locally and by a non-commercial entity.

What requirements will be placed on such vaccines for local registration: requirements for the demonstration of efficacy, the establishment of manufacturing practice etc. ?

In considering the future of tick vaccines, two issues are intimately linked and both must be solved: the demonstration of scientific feasibility and the issue of manufacture and delivery of a vaccine