Barbervax: the first commercially available sub-unit vaccine for a nematode parasite.

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Moredun Research Institute

Mission: *"To lead in livestock health solutions for global food security"*

1920

2015

Haemonchus contortus

(Barbers Pole worm)

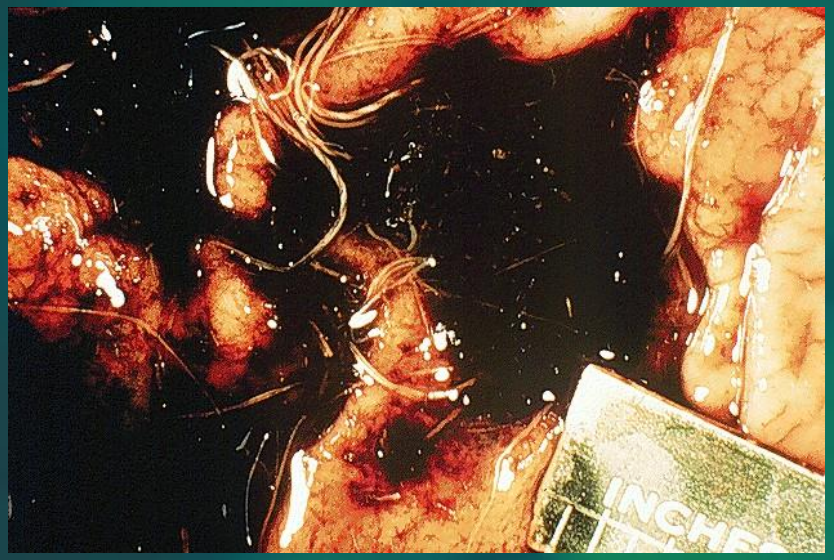
Globally, the most important nematode parasite of sheep and goats

Blood sucker

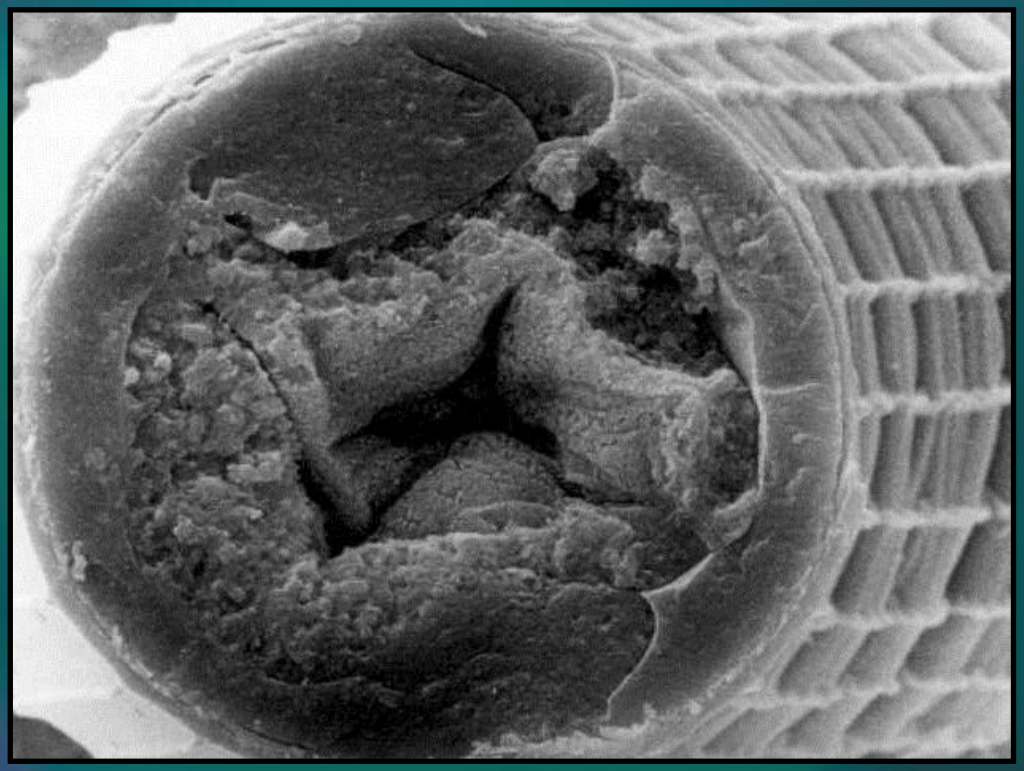
Prefers warm climates

Resistance to drugs a serious problem

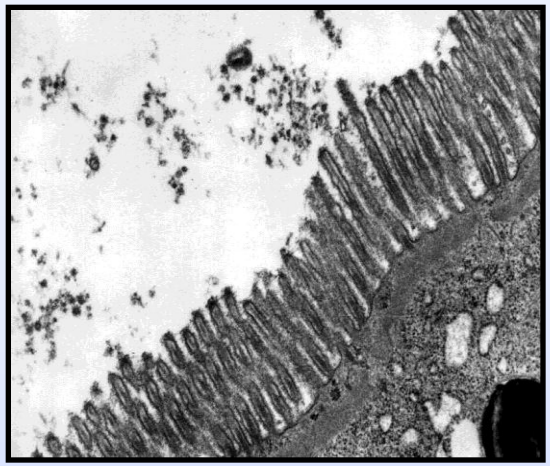
No vaccine available for this or any other species of gut worm of any host – until Barbervax was launched 6 months ago!



Vaccine mechanism

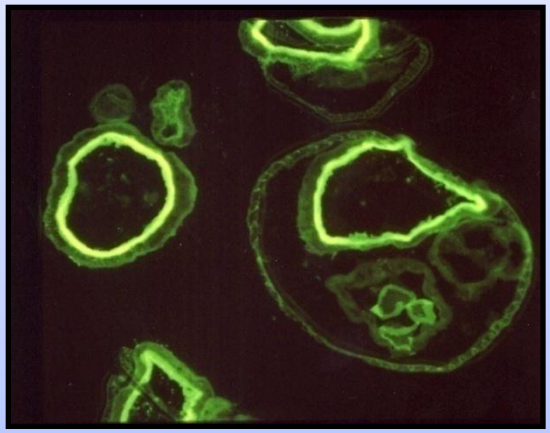


Because Haemonchus feeds on blood, molecules on the surface of its intestinal cells are suitable targets for a vaccine



When surface proteins from the brush border of the worms intestinal cells are injected into a sheep…..

it responds and makes antibodies which circulate. in the blood. If a vaccinated sheep gets infected, the parasites ingest blood so that antibodies bind to the worms intestines …



….leading to greatly reduced egg output and worm numbers……

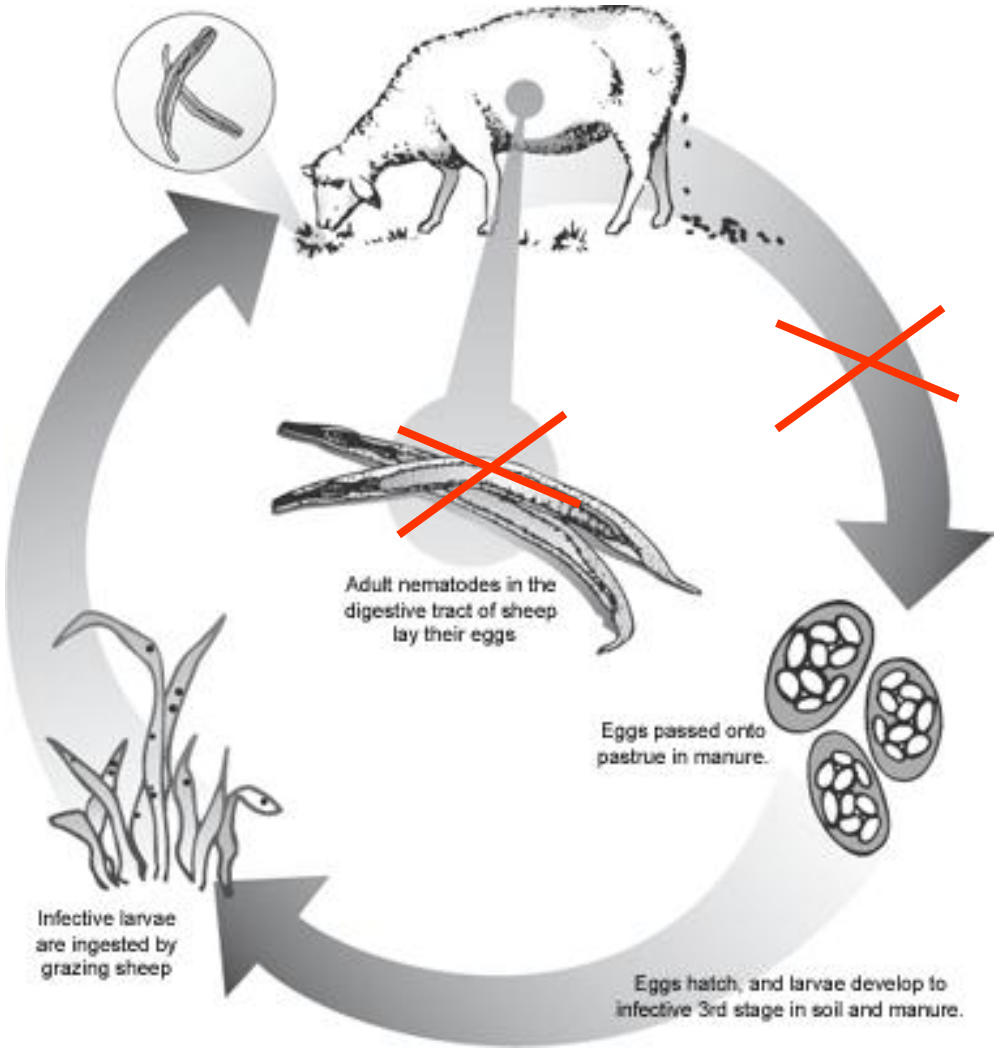
H11 and H-gal-GP antigens give best protection for any nematode in any host

e.g. Moredun's H-gal-GP in Quil A

- 9 different experiments.
- 82 lambs, aged 2-10 months.
- Challenged 1 x 5,000 *Haemonchus*.
- Protection (%)

	eggs	worms
mean	**95.0**	**70.4**
SD	2.6	8.1

Vaccine to kill blood feeding worm stages and reduce egg laying?



No amplification during ex-host period:

Potential to reduce transmission of disease

The gut antigens are mainly digestive proteases

- “H11”, a family of leucine aminopeptidases (Babraham).
- “H-gal-GP”, a complex of aspartyl and metallo –proteases (Moredun).
- Both highly protective in native form individually and/or in combination.

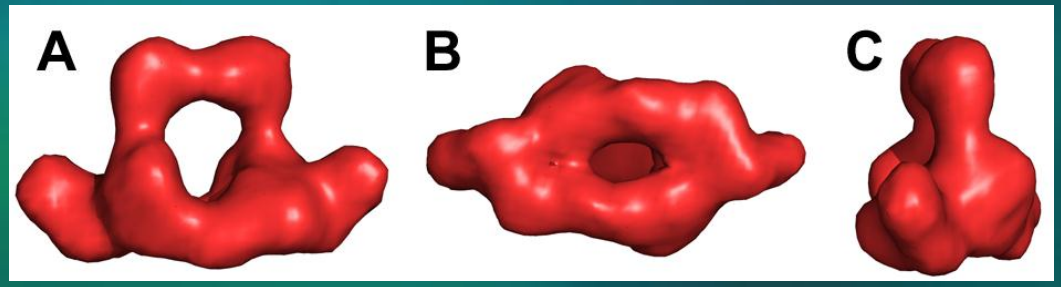
H-gal-GP and H11 are “hidden” antigens.

- Advantages:
  - Vaccine works and in all classes of sheep
  - Worms have not evolved to cope
  - Conserved antigens – no “strains”
  - Likely to be sustainable

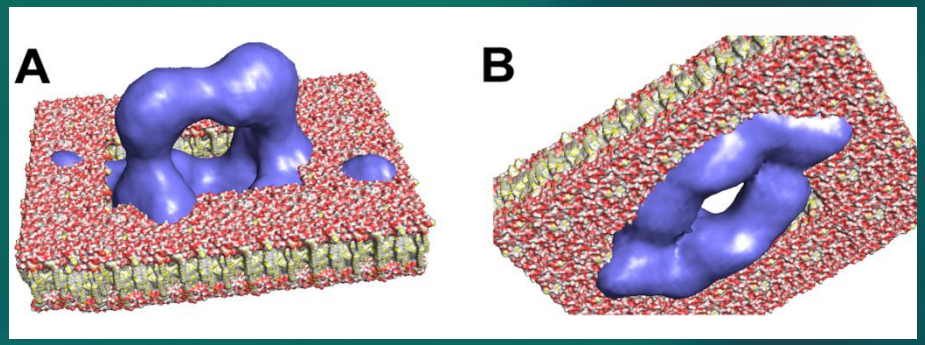
- Disadvantages:
  - Response not boosted by challenge infection
  - Repeated vaccination necessary

Structure of H-gal-GP complex by EM

(J. Trinick and S. Meunsch, Leeds University)



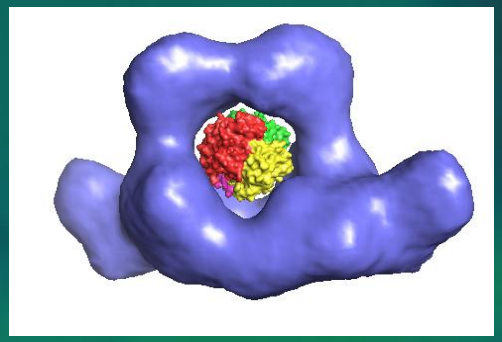
Slightly smaller than FMD virus



Orientation in the membrane?

Albumin and Hb fit Into the cavity.

A protease machine?

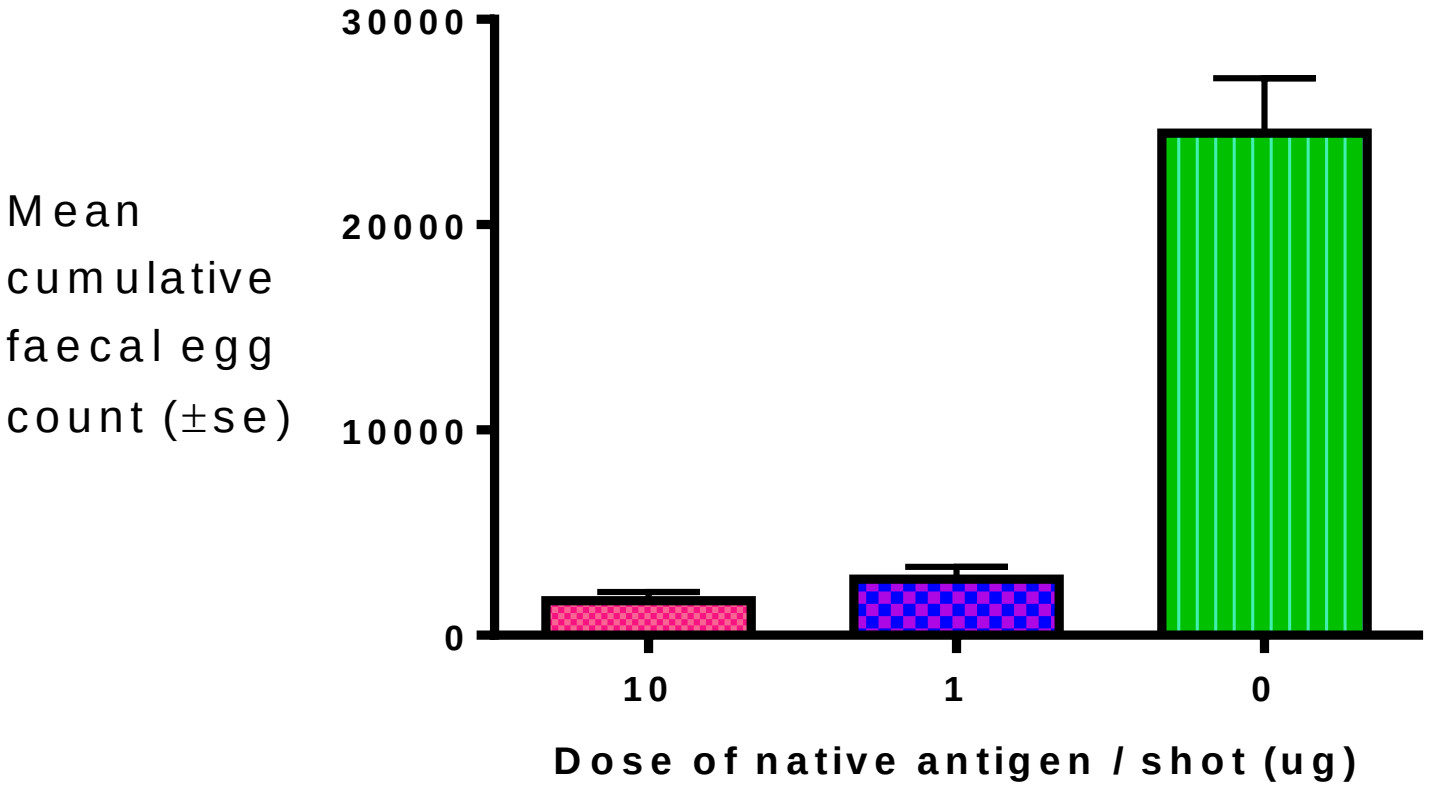


Could antibodies block substrate access to the protease machine?

Neither H-gal-GP, nor H11 are protective if unfolded or in recombinant form!

Since no protection with recombinant proteins, would a low dose of native antigen work?

Low dose vaccine trial in Moredun sheep



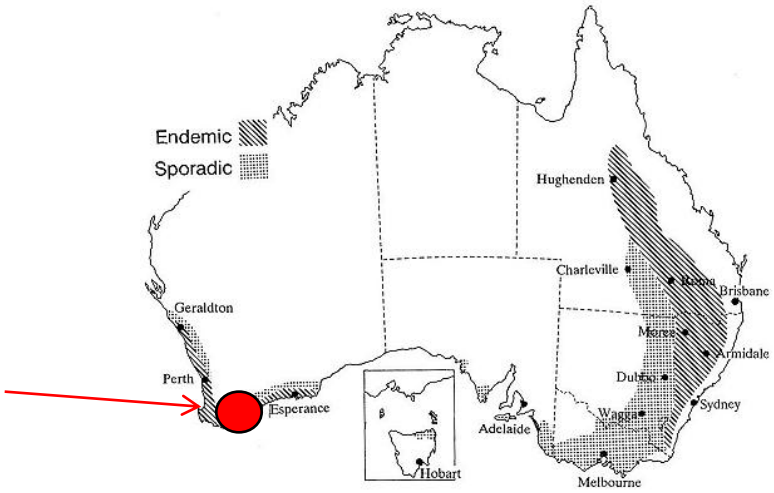
This dose is small enough for a native antigen vaccine to be commercially viable if large numbers of clean adult *Haemonchus* can be obtained cost-effectively

Manufacture of Barbervax in Australia

Where?

(must be from Australian *Haemonchus*)

Dept of Agriculture and Food, Albany, W.A



How?

Vaccine culture system and bio-fermenter?

Ours is unusual, it can walk and is edible!

Advantages

1. Cost effective
2. Readily scaled-up!

Commercial Scale Barbervax Manufacture

(Albany, Western Australia)

Expression system: *Haemonchus contortus*
Large scale fermenter : *Ovis aries*

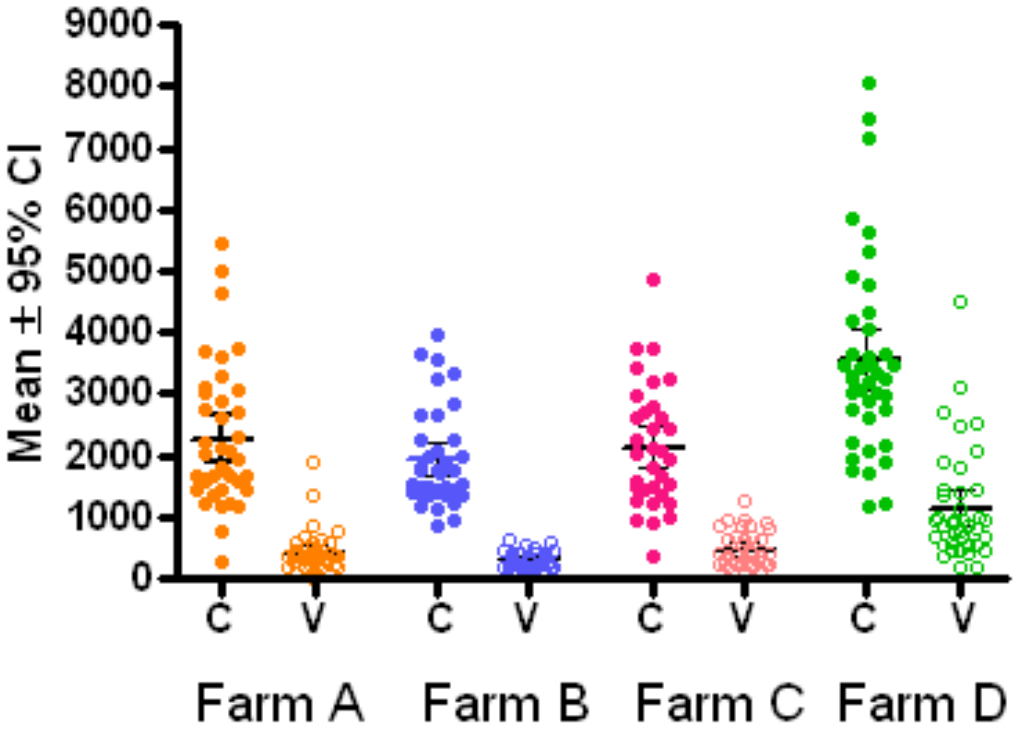
Who needs molecular biology when a cement mixer will do?!

Commercial Scale Vaccine Manufacture

Good Manufacturing Practice Licence 2011

Field trials with lambs in Australia

Effect of vaccine on Haemonchus egg output on four NSW farms from early Nov 2011 to late April 2012



80% overall reduction in egg count in vaccinates

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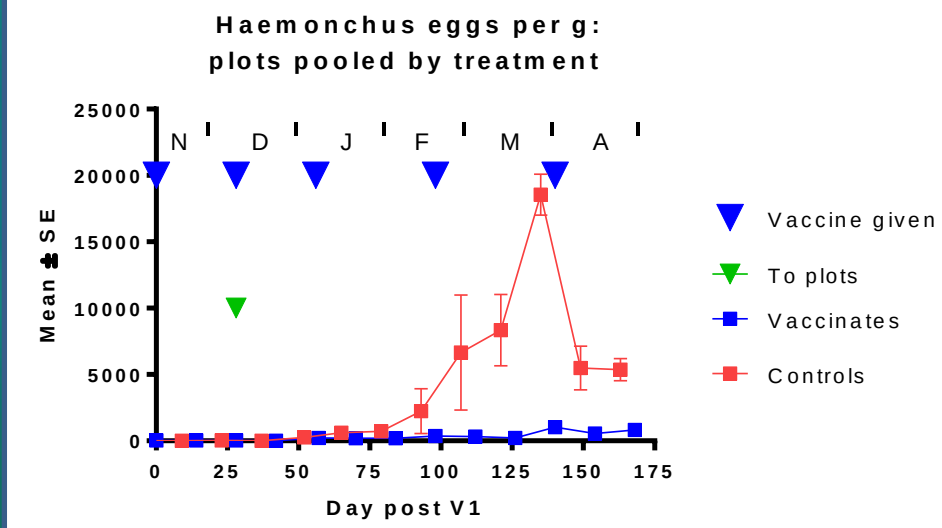
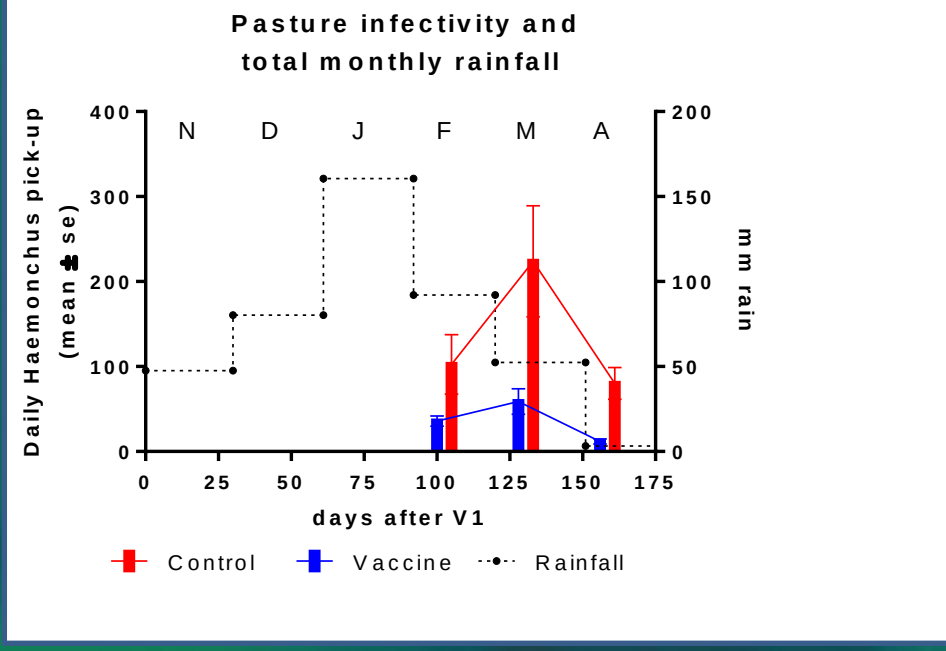
Replicate plot field trials with lambs in NSW, Australia.

Performed independently by CSIRO or VHR

Vaccinates and controls grazing separately

Tracer lambs





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Vaccinating ewes

Around lambing time and during lactation naturally acquired immunity to nematodes wanes – higher egg counts – the so-called periparturient rise.

This egg output is important epidemiologically as it is the source of infection for the next generation of lambs

Could Barbervax reduce this periparturient rise?

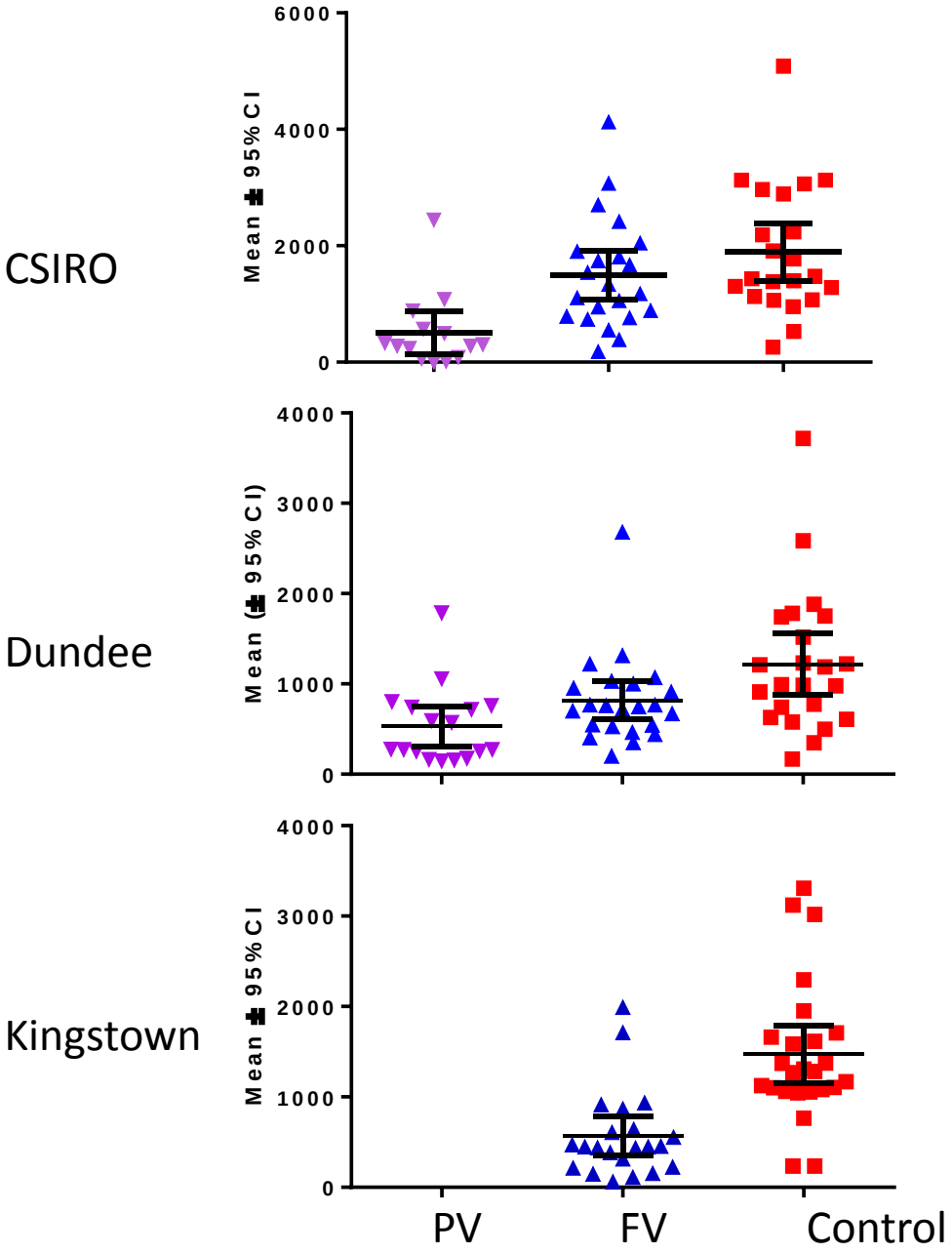
Ewe trial design

Would the vaccine reduce the periparturient rise?

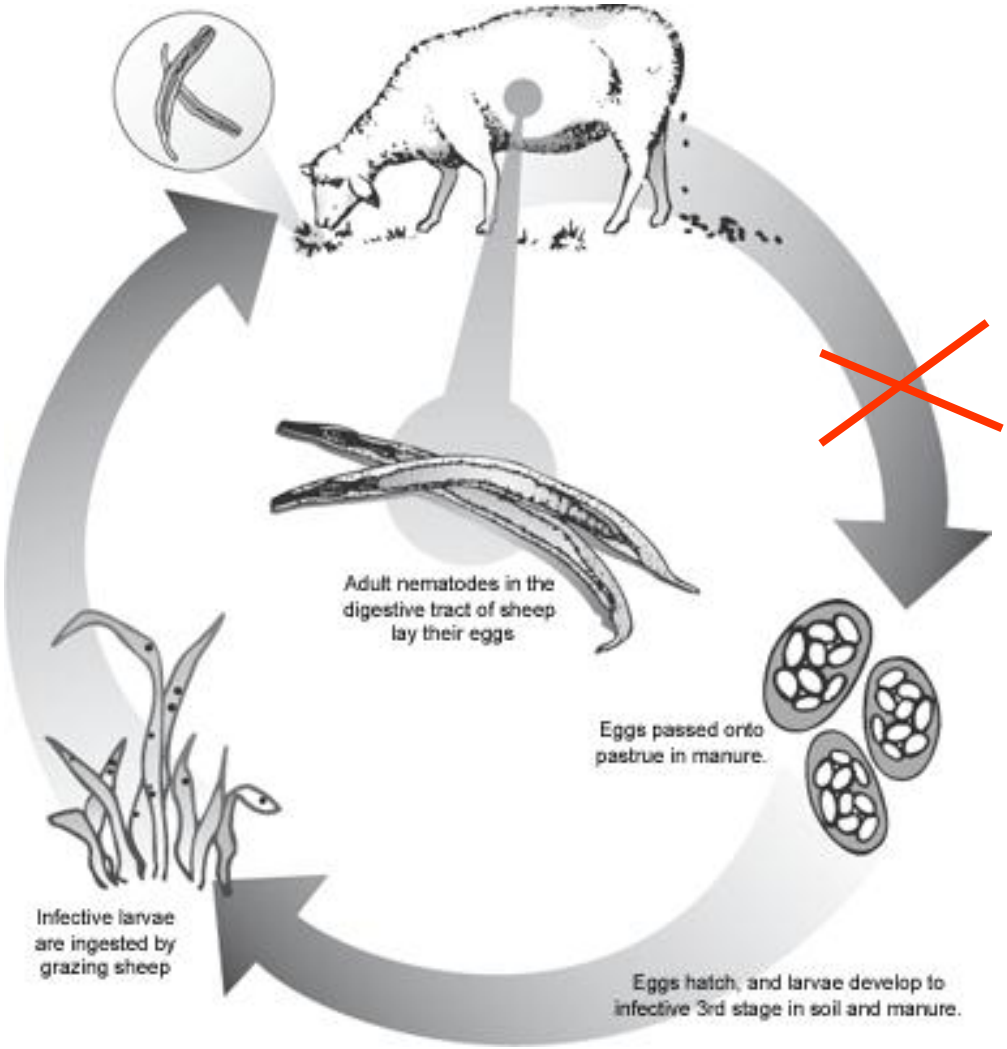
Group (all grazing together)	**Vaccination schedule**		
	6-8 weeks before lambing	1-2 weeks before lambing	At lamb marking, then at 6 week intervals
First vaccinated	+	+	+
Previously vaccinated as lambs and hoggets	-	+	+
Control	-	-	-

- egg counts and anaemia every two weeks
- precautionary drench if PCV<22% or epg>10,000
- 3 trials

Individual ewe *Haemonchus* egg counts averaged over lactation



How protective does a *Haemonchus* vaccine need to be?



No amplification during ex-host period:

Modelling the epidemiological benefit relative to a conventional anthelmintic control programme

Dobson RJ, et al 2011. A multi-species model to assess the effect of refugia on worm control and anthelmintic resistance in sheep grazing systems. *Aust Vet J*., 2011 89:200–208.

How good does a *Haemonchus* vaccine have to be in lambs?

Vaccine protection	% Deaths	mean yr. to AR	*Haemonchosis** years
90%	0.2	16.5	1/20
85%	0.5	16.7	1/20
80%	**0.6**	**17.3**	**1/20**
75%	0.9	17.3	1/20
70%	1.6	18.7	2/20
65%	4.5	19.8	5/20
60%	9.3	20.0	9/20
55%	15.6	20.7	9/20
50%	19.3	20.8	9/20
Unvaccinated	**27.7**	**11.5**	**8/20**

Vaccinated lambs received one anthelmintic treatment and theoretical vaccines with protection ranging from 90-50%.

Unvaccinated lambs received four anthelmintic treatments.

*Haemonchosis = the number of years out of 20 in which lamb deaths, caused by H. contortus, were 3% or more.

Vaccinating ewes benefits their lambs

Level of protection* induced by the vaccine		BENEFIT TO LAMBS		
		%Deaths	Mean *H.c.* epg	Haemonchosis years/20
Ewe	Lamb			
50-80%	70%	5.9	310	4.0
0%	0%	32.3	955	10.0

Vaccinating ewes benefits their lambs as well as themselves

Level of protection* induced by the vaccine		%Deaths	Mean *H.c.* epg	Haemonchosis years/20
Ewe	Lamb			
BENEFIT TO LAMBS				
50-80%	70%	5.9	310	4.0
0%	0%	32.3	955	10.0
BENEFIT TO EWES				
50-80%	70%	1.2	86	2.3
0%	0%	18.5	270	8.0

Barbervax profile

- 5ug native antigen + 1mg saponin adjuvant /dose
- 1ml injection under the skin. 250ml packs.
- Shelf life at least 2.5 years at 2-8°C.
- 5 doses for lambs during the summer *Haemonchus* risk period
- 4/5 doses for older sheep if vaccinated in previous summers.
- Reduces the periparturient rise – epidemiological benefit to flock
- Works versus all *Haemonchus* including drench resistant worms.
- Sustainable - vaccine resistance unlikely to develop.
- Non toxic. “Green”.
- Slows the development of anthelmintic resistance in all species

- No effect against scour worms.

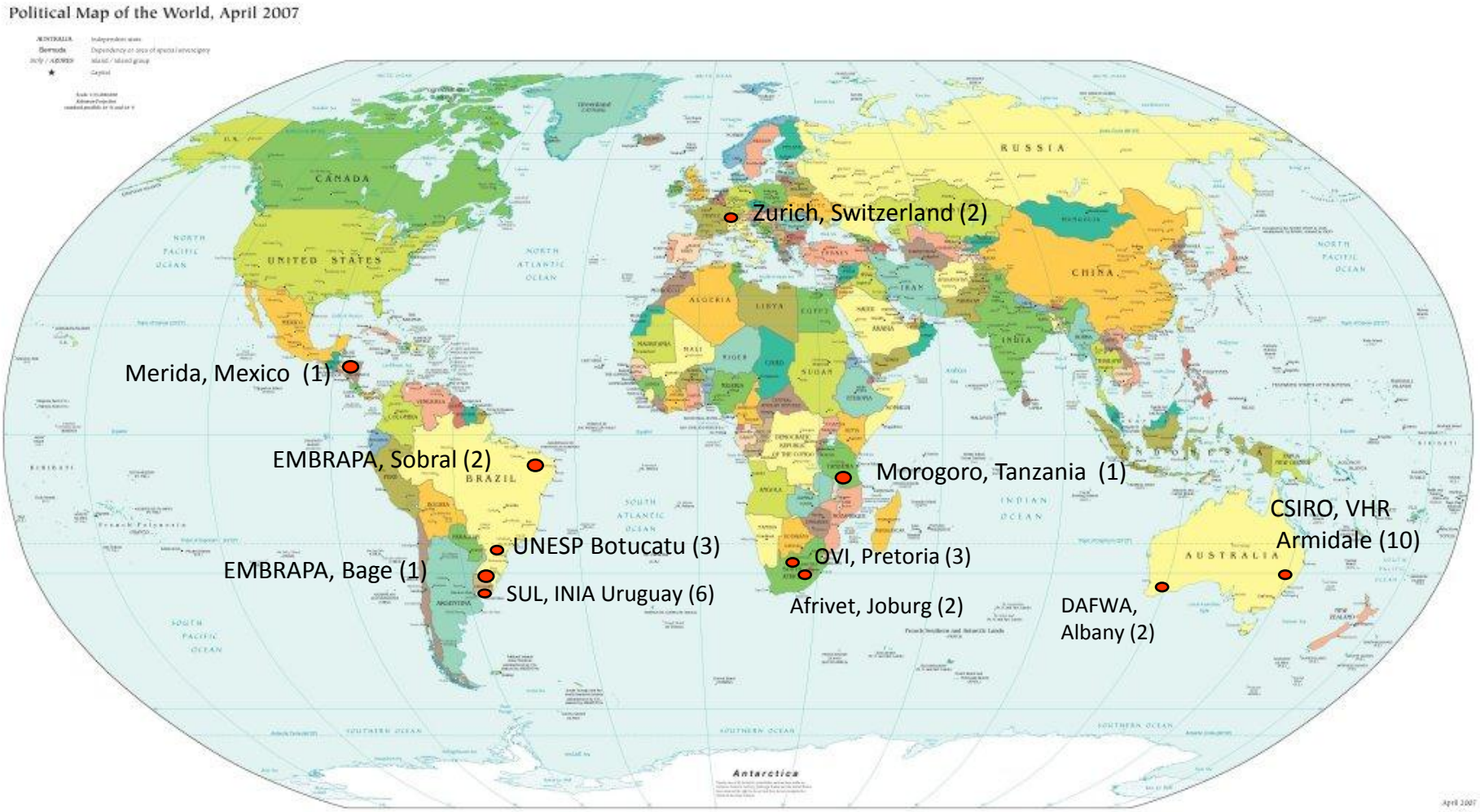
Armidale, New South Wales, Australia

APVMA Registered October 1st , 2014

All 300,000 doses of vaccine sold by word of mouth within 10 days

No large pharma involved

Haemonchus vaccine field trials (33)



Potential Global Impact on Livestock

Nelore cattle
In Brazil

Boer Goats, South Africa

Sheep and goats, Tanzania

Bergamasco ewes, Brazil

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Barbervax is an unusual vaccine

1. Sub-unit native antigen vaccine for a metazoan parasite

2. A “hidden” antigen vaccine

4. Manufactured by a research institute - no pharmas involved.

5. No share holders – profits re-invested in research

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