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

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Moredun Research Institute, Edinburgh, UK.
Moredun Research Institute

Mission: “To lead in livestock health solutions for global food security”
**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 (%)
  
<table>
<thead>
<tr>
<th></th>
<th>eggs</th>
<th>worms</th>
</tr>
</thead>
<tbody>
<tr>
<td>mean</td>
<td>95.0</td>
<td>70.4</td>
</tr>
<tr>
<td>SD</td>
<td>2.6</td>
<td>8.1</td>
</tr>
</tbody>
</table>
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).
- 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 Barbersvax 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
Replicate plot field trials with lambs in NSW, Australia.

Performed independently by CSIRO or VHR

Vaccinates and controls grazing separately

Tracer lambs
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?

<table>
<thead>
<tr>
<th>Group (all grazing together)</th>
<th>Vaccination schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>6-8 weeks before lambing</td>
</tr>
<tr>
<td>First vaccinated</td>
<td>+</td>
</tr>
<tr>
<td>Previously vaccinated</td>
<td>-</td>
</tr>
<tr>
<td>as lambs and hoggets</td>
<td>-</td>
</tr>
<tr>
<td>Control</td>
<td>-</td>
</tr>
</tbody>
</table>

- 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

![Graphs showing mean Haemonchus egg counts with 95% CI for different locations: CSIRO, Dundee, and Kingstown, with categories PV, FV, and Control.](image-url)
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

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

<table>
<thead>
<tr>
<th>Vaccine protection</th>
<th>% Deaths</th>
<th>mean yr. to AR</th>
<th>Haemonchosis* years</th>
<th>Vaccinated lambs received one anthelmintic treatment and theoretical vaccines with protection ranging from 90-50%.</th>
</tr>
</thead>
<tbody>
<tr>
<td>90%</td>
<td>0.2</td>
<td>16.5</td>
<td>1/20</td>
<td></td>
</tr>
<tr>
<td>85%</td>
<td>0.5</td>
<td>16.7</td>
<td>1/20</td>
<td></td>
</tr>
<tr>
<td>80%</td>
<td><strong>0.6</strong></td>
<td><strong>17.3</strong></td>
<td><strong>1/20</strong></td>
<td></td>
</tr>
<tr>
<td>75%</td>
<td>0.9</td>
<td>17.3</td>
<td>1/20</td>
<td></td>
</tr>
<tr>
<td>70%</td>
<td>1.6</td>
<td>18.7</td>
<td>2/20</td>
<td></td>
</tr>
<tr>
<td>65%</td>
<td>4.5</td>
<td>19.8</td>
<td>5/20</td>
<td></td>
</tr>
<tr>
<td>60%</td>
<td>9.3</td>
<td>20.0</td>
<td>9/20</td>
<td></td>
</tr>
<tr>
<td>55%</td>
<td>15.6</td>
<td>20.7</td>
<td>9/20</td>
<td></td>
</tr>
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<td>50%</td>
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<td>20.8</td>
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Unvaccinated: 27.7 11.5 8/20

*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

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<tr>
<th>Level of protection* induced by the vaccine</th>
<th>BENEFIT TO LAMBS</th>
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<tr>
<td>Ewe</td>
<td>Lamb</td>
<td>%Deaths</td>
<td>Mean H.c. epg</td>
<td>Haemonchosis years/20</td>
</tr>
<tr>
<td>50-80%</td>
<td>70%</td>
<td>5.9</td>
<td>310</td>
<td>4.0</td>
</tr>
<tr>
<td>0%</td>
<td>0%</td>
<td>32.3</td>
<td>955</td>
<td>10.0</td>
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* Level of protection refers to the effectiveness of the vaccine in protecting the ewes and their lambs against Haemonchosis.
Vaccinating ewes benefits their lambs as well as themselves

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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
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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