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# Helminth Vaccines in Ruminants

## From Development to Application



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### KEYWORDS

• Gastrointestinal nematodes • Lungworm • Liver fluke • Vaccines

### KEY POINTS

- Only a few vaccines against parasitic helminths of livestock are currently on the market; namely those against *Dictyoacaulus viviparus* in cattle, *Haemonchus contortus* in sheep, and the tapeworm *Echinococcus granulosus* in sheep.
- Research is ongoing to develop vaccines based on purified or recombinantly expressed worm proteins for *Ostertagia ostertagi* and *Cooperia oncophora* in cattle, for *Teladorsagia circumcincta* and *H contortus* in sheep, and for *Fasciola hepatica* in ruminants.
- Recombinant expression of worm antigens with the correct conformation to induce protective immunity is still a major challenge in vaccine development.
- Vaccination is likely to be part of integrated worm control, together with other control measures, such as anthelmintic treatments, biological control, and grazing management.
- Interdisciplinary research, including social sciences, should investigate drivers of farmers' and veterinarians' decision making, to optimize uptake of vaccination by the end users.

### INTRODUCTION

The major helminth infections in ruminants include gastrointestinal (GI) nematodes, liver fluke, and lungworms. At present, they are mainly controlled by regular treatments with anthelmintic drugs. However, decades of intensive use of anthelmintics have led to the development of anthelmintic resistance. High levels of resistance against all classes of anthelmintics are reported in GI nematodes of small ruminants worldwide. Resistance against macrocyclic lactones is also emerging in cattle parasites, mainly in *Cooperia* spp and, to a lesser extent, *Ostertagia ostertagi*. Resistance against flukicides has been reported in *Fasciola hepatica* in several countries.

Together with a more sustainable use of anthelmintics, potential alternative (or complementary) control methods include bioactive forages, selective breeding for host resistance or resilience, nematophagous fungi, and vaccines.<sup>1</sup> Vaccines are

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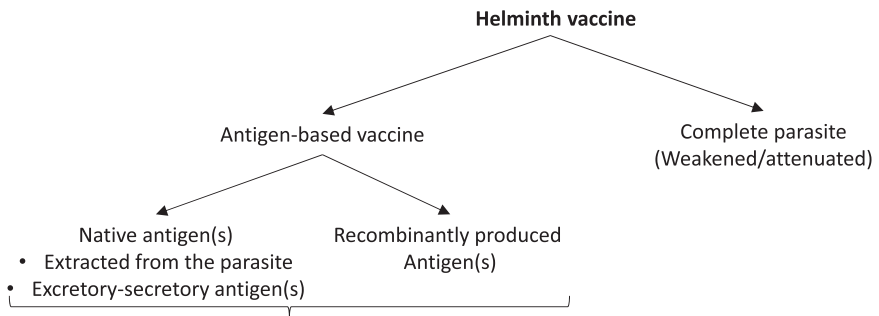
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considered a favorable option, because of the durable protection they can provide and a lack of chemical residues in animal products and the environment.<sup>2</sup> The principle of vaccination is to induce immunologic protection in a host against a subsequent infection. For this, the immune system can be stimulated with either the weakened or killed pathogen or proteins/antigens from it, the so-called subunit vaccines (Fig. 1). Subunit vaccines can be based on a single antigen or a mixture of antigens, which can be purified from the parasites or produced through recombinant DNA technology. The approach of producing a commercial vaccine straight from worm material is not applicable for most parasite species because it is practically difficult or even impossible to obtain large enough quantities of parasite material. For this reason, recombinant vaccines have been evaluated against a range of helminths. However, maintaining the correct conformation of target antigens in recombinant form is a major challenge,<sup>3</sup> and only a few recombinant vaccine antigens have been shown to be protective. The challenge for further development lies in delivering these promising subunit vaccines in a manner feasible for large-scale commercial production, testing their efficacy in more extensive field trials, and in making them fit for purpose for commercial and end-user uptake.<sup>2</sup>

Despite strong efforts to develop antiparasitic vaccines, only 3 vaccines are currently on the market (Table 1 for specifications): (1) a live attenuated vaccine for control of the bovine lungworm, *Dictyocaulus viviparus* (Bovilis Huskvac, MSD Animal Health); (2) a native gut antigen-based vaccine, recently launched for the control of haemonchosis in sheep in Australia (Barbervax, Wormvax Australia Pty Ltd) and South Africa (Wirevax, Afrivet Business Management Pty Ltd); and (3) a cestode vaccine



- **'Hidden' antigen:** antigen from the parasite that is typically not exposed to the immune system during the course of an infection, for example antigens from the gut of the worm.
- **'Conventional' antigen:** antigen that is typically exposed to the immune system of the host during an infection, for example the excretory-secretory proteins from a worm.
- **Excretory-secretory antigen:** antigen released in culture fluid by worms cultured *in vitro*
- **Somatic antigen:** antigen extracted from water-soluble or insoluble (fractions of) whole worm homogenate

Fig. 1. Different types of helminth vaccine antigens.

(Providean Hidatil EG95, Tecnovax) is available on the commercial market in parts of South America for the control of *Echinococcus granulosus* in sheep and goats.

This article summarizes the state of the art in vaccine research against sheep and cattle helminths, including the lungworm *D viviparus*, the GI nematodes *Haemonchus contortus*, *Teladorsagia circumcincta*, *O ostertagi*, and *Cooperia oncophora*, and the liver fluke *F hepatica*. Furthermore, safety and efficacy requirements for implementation of helminth vaccines in field conditions are discussed, as well as factors that may affect uptake of vaccines by the end users.

## STATE OF THE ART IN VACCINE DEVELOPMENT

### *Dictyoaulus viviparus*

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A commercial lungworm vaccine (Bovilis Huskvac, MSD Animal Health), composed of live irradiated third-stage (L3) *D viviparus* larvae, was developed decades ago.<sup>4</sup> Two doses of 1000 viable irradiated larvae are delivered orally with an interval of approximately 4 weeks, and the full vaccination schedule should be completed at least 2 weeks before turnout of the vaccinated animals on pasture. Vaccinated cattle should not be treated with anthelmintics until at least 2 weeks after the second vaccination. The vaccine can be used in healthy cattle of 8 weeks of age or older, which includes grazing young stock and adult cows. Although vaccine-induced protection is generally good,<sup>5</sup> the vaccine has disadvantages associated with live vaccines, such as ethical issues (production of larvae in donor animals), batch heterogeneity, and a short shelf life. In an attempt to overcome these issues, several attempts were made to develop recombinant subunit vaccines, with limited success. Vaccination with recombinant acetylcholinesterase,<sup>6</sup> paramyosin,<sup>7,8</sup> or asparaginyl peptidase legumain-1<sup>9</sup> with different adjuvants did not result in significant and/or reproducible reduction in worm numbers or larval shedding.

### *Haemonchus contortus*

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An *H contortus* vaccine based on a worm gut membrane antigen mixture was recently commercialized for sheep (Barbervax, Wirevax) and has quickly become an invaluable tool to control haemonchosis in areas where anthelmintic resistance is rampant.<sup>10</sup> The vaccine is only registered in Australia and South Africa, but it can be used in the United Kingdom under Special Treatment Certificate and veterinary prescription. Vaccination with the vaccine also conferred protection against *Haemonchus placei* in grazing calves,<sup>11</sup> but the vaccine has not been registered for use in cattle. Vaccination of young goats did not sufficiently protect against *H contortus* infections on pasture.<sup>12</sup> For the production of this vaccine, the native antigens need to be extracted and purified locally from adult *H contortus* derived from infected sheep. A vaccine based on recombinantly expressed antigens would have advantages compared with a native antigen vaccine for reproducibility of product batches, biosafety, and global distribution. Many efforts have been made to identify and express a range of antigens from *H contortus*, but most recombinant proteins were unsuccessful in eliciting protective immunity.<sup>2,10</sup> Recently, a gene encoding an Hc23 somatic antigen was identified and expressed in *Escherichia coli*. Lambs vaccinated with the recombinant Hc23 antigen were significantly protected against an artificial challenge infection, with more than 80% reduction in fecal egg counts (FECs) and average abomasal parasite burdens, compared with challenge controls.<sup>13</sup> This work is a promising step toward a recombinant *Haemonchus* vaccine, but further experiments are needed to confirm these results and to test the vaccine in natural infection conditions.

**Table 1**  
Commercialized vaccines against helminth parasites in ruminants

Brand Name	Parasite	Animal Species	Antigen	Adjuvant	Administration Route	Vaccination Schedule	Level of Protection	Withdrawal Period
Bovilis Huskvac	<i>Dictyocaulus viviparus</i>	Cattle	Live irradiated third-stage larvae	None	Oral	Basic scheme: 2 vaccinations with 4-wk interval before turnout Revaccination: single dose before turnout	95%–98% (worm burden)	None
Barbervax, Wirevax	<i>Haemonchus contortus</i>	Sheep	Gut membrane proteins	Saponin	Subcutaneous	Basic scheme: 3 vaccinations with interval of 3–4 wk before <i>Haemonchus</i> season Revaccination: 6-wk intervals	93%–95% (egg counts) 72%–94% (worm burden)	None
Providean Hidatil EG95	<i>Echinococcus granulosus</i>	Cattle, sheep, goats, camelids	EG95	Montanide and saponin	Subcutaneous or intramuscular	2 vaccinations with 1-mo interval	95%–100% (cysts)	None

### ***Teladorsagia circumcincta***

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Similar to *H. contortus*, over the years several antigens have been evaluated as vaccine candidates against the sheep abomasal parasite *T. circumcincta*.<sup>2</sup> The most promising results have recently been obtained with an experimental vaccine that is based on a cocktail of 8 recombinant proteins. The native versions of these antigens were originally identified either as immunodominant excretory/secretory proteins or selected because of their potential immune modulatory role or as homologues of vaccine candidates in related nematode species.<sup>2</sup> All proteins were expressed in *E. coli* or the yeast *Pichia pastoris*. Vaccination with this antigen cocktail with Quil A adjuvant protected 6-month-old to 7-month-old lambs and periparturient ewes against a challenge infection, resulting in significantly reduced FECs (73%–92% reduction in lambs, 45% in ewes) and worm burdens (56%–75% reduction in lambs).<sup>14,15</sup> Work is ongoing to refine the protein cocktail by testing fewer recombinant protein combinations in vaccine trials.<sup>16</sup> Further, its protective capacity will be tested in newly weaned lambs and in field trials.

### ***Ostertagia ostertagi***

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Over the last 40 years, several antigens and antigen mixtures have been evaluated against *O. ostertagi* (reviewed in Rinaldi and Geldhof<sup>17</sup>). At present the most promising experimental vaccine against *O. ostertagi* is based on activation-associated secreted proteins (ASPs).<sup>2,18</sup> Vaccination with a fraction of the adult excretory-secretory products containing ASP or with the purified protein has consistently resulted in a significantly reduced worm egg output (55%–62% reduction) after artificial trickle challenge infections.<sup>18–21</sup> Attempts to generate similar levels of protection with a recombinant ASP protein have been unsuccessful so far. Recombinant proteins, expressed in different expression systems, such as *E. coli*, insect cells, and *P. pastoris*, were either insoluble or did not protect vaccinated calves against challenge infection.<sup>3,22</sup> Current research focuses on eliciting differences in protein folding and glycosylation between the native and recombinant ASP proteins, to identify epitopes that are important to induce a protective immune response.<sup>23,24</sup>

### ***Cooperia oncophora***

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Based on the promising results obtained with an ASP-based vaccine against *O. ostertagi*, a double-domain ASP (ddASP) protein purified from the excretory-secretory material of adult *C. oncophora* worms was recently successfully evaluated as a vaccine candidate.<sup>25,26</sup> Immunization with this antigen resulted in a significant reduction (91%) in cumulative FEC in an experimental challenge experiment. In a subsequent field trial, *C. oncophora* cumulative FECs in vaccinates were reduced by 59%, resulting in 65% less infective *C. oncophora* larvae on plots grazed by vaccinated calves and a significant reduction of 82% in worm counts in the vaccinates at housing.<sup>26</sup> Vaccination with the *C. oncophora* ddASP also protected calves against a challenge infection with an Uruguayan isolate of mixed *C. oncophora* and *Cooperia punctata*, suggesting that the protective epitopes are conserved between *Cooperia* species/isolates in different parts of the world. In contrast, the *C. oncophora* ddASP vaccine did not protect sheep against *Cooperia curticei* (unpublished results). As with *O. ostertagi*, the research is currently focused on the recombinant expression of the ASP in an immune-active form.

### ***Fasciola Spp***

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An overview of individual antigens and combinations thereof that have been tested against the liver flukes *F hepatica* and *Fasciola gigantica* in cattle and sheep is given by Toet and colleagues.<sup>27</sup> Some antigens, such as cathepsin L1 and leucine aminopeptidase (LAP), induced significant protection levels in sheep and/or cattle, both as native, purified antigen and as recombinant protein. However, protection levels were highly variable, hence the need to test each vaccine in multiple vaccine trials to show consistent protection.<sup>27</sup> Combining different antigens, such as cathepsins, with LAP or hemoglobin, or vaccination with a chimeric protein composed of leucine aminopeptidase and cathepsin L1 has not substantially improved vaccine efficacy.<sup>27,28</sup> Despite multiple individual studies showing promising results for various DNA vaccine candidates against fascioliasis in animal models, a systematic review and meta-analysis did not show a significant pooled efficacy for all vaccine candidates against fasciola infection.<sup>29</sup>

### **VACCINE SAFETY, EFFICACY, AND USE OF VACCINES IN PARASITE CONTROL**

The ideal parasitic vaccine should be safe, have a high efficacy, and ideally this activity should extend to a wide range of parasites.<sup>30</sup>

#### ***Vaccine Safety***

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Safety is an absolute requirement for any new vaccine. To avoid unwanted contamination with other proteins or pathogens and to ensure batch reproducibility, recombinant protein or DNA vaccines would be preferable to vaccines consisting of native proteins, purified from worms that are collected from animals. Vaccination with a (recombinant) protein (cocktail) in combination with a well-defined commercial adjuvant is not expected to raise important safety issues. Nevertheless, the development of a human hookworm vaccine based on ASPs caused allergic reactions in vaccinated preexposed individuals.<sup>31</sup> Several vaccines currently under experimental evaluation for livestock helminths also contain ASPs (*O ostertagi*, *C oncophora*, *T circumcincta*). No side effects were observed in calves that were vaccinated with a double-domain ASP from *C oncophora* before turnout on pasture,<sup>26</sup> but it has not been tested yet whether this vaccine is safe to use in regions with year-long grazing, where animals are likely to be infected before vaccination. However, Nisbet and colleagues<sup>15</sup> observed no adverse reactions in grazing ewes that were vaccinated with a recombinant *T circumcincta* vaccine containing ASP.

#### ***Vaccine Efficacy***

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The major aim in controlling helminth infections by vaccination is to reduce parasite transmission by decreasing the number of viable eggs that are excreted into the environment, because these determine the number of infective larvae on the pasture later in the grazing season. The fecundity of *Ostertagia* is highly regulated by host immunity,<sup>32</sup> and fecal egg output can be strongly reduced without a reduction in worm numbers.<sup>33</sup> In contrast, the fecundity of *Haemonchus* is not regulated by the intensity of the infection and there is a good correlation between total daily FECs and mature female worm burden.<sup>34</sup> Consequently, to prevent the buildup of a high pasture infection level, a *Haemonchus* vaccine needs to reduce the number of adult worms present in the animals early in the grazing season, either by reducing the establishment of infective larvae or by increasing the mortality of established worms.<sup>30</sup>

An advantage of vaccines based on hidden antigens (see [Fig. 1](#)) is that they can produce protective effects in situations in which natural immunity is either weak or

ineffective, such as in young lambs or in periparturient ewes. A disadvantage is that vaccine-induced immunity is not boosted by a challenge infection, because the hidden antigens in the ingested worms are not exposed to the host's immune system. As a consequence, immunity induced by vaccination with hidden antigens is typically short lasting and animals need to be revaccinated regularly. This need is shown by the vaccination schedules for *H contortus* in sheep. When lambs first receive Barbervax, 3 doses of the vaccine with intervals of 3 to 4 weeks are required to reach an effective level of antibodies, whereas subsequent vaccinations are given each 6 weeks until *H contortus* infections are no longer a risk ([www.wormboss.com.au](http://www.wormboss.com.au)).

Animals vaccinated with conventional antigens (see [Fig. 1](#)) benefit from restimulation of their immune systems by the corresponding antigens from the challenge infection. The level and duration of protection required depend on the local grazing management and climate conditions.<sup>35</sup>

In sheep, both lambs and their dams need to be vaccinated. The ewes contribute significantly to the pasture infection because of their periparturient increase in egg shedding, and the lambs are vulnerable because of a lack of acquired immunity. Therefore, experimental *T circumcincta* vaccines are tested in both these age categories,<sup>14,15</sup> and separate vaccine schedules were designed for lambs and ewes for the commercial *H contortus* vaccine ([www.barbervax.com.au](http://www.barbervax.com.au)).

In dairy cattle, calves are typically separated from their dams at birth and the heifer calves are raised as a separate group of replacement stock. First grazing season calves are the most susceptible to infections with GI nematodes, and parasitic gastroenteritis is mainly seen in this age class when no appropriate preventive measures have been taken. In many parts of Europe, there is a well-defined grazing period, from spring to autumn. Helminth-naive calves should be vaccinated before turnout and the vaccine should protect them until natural immunity has sufficiently developed. Natural immunity against *C oncophora* develops within the first months of grazing, but immunity development against *O ostertagi* is slow,<sup>36</sup> and vaccination should protect calves during their entire first grazing season. Because the peak egg output occurs around 2 months after turnout,<sup>37</sup> it can be anticipated that reduction of worm egg shedding in the first 2 to 3 months after turnout may be sufficient to prevent accumulation of infective larvae on pasture and to protect vaccinated animals until housing in autumn.<sup>35</sup> The authors previously suggested that a vaccine that reduces the mean fecal egg output by around 60% during the first 2 months after turnout would sufficiently protect calves against GI nematodes during their first grazing season and allow them to develop a natural immunity without production loss.<sup>30</sup> For *C oncophora*, this has been shown to be an achievable goal,<sup>26</sup> but whether this assumption holds for *O ostertagi* in field conditions remains to be confirmed. Moreover, this expectation does not take into account individual variability of each calves' response to vaccination.

Required levels of vaccine efficacy and duration of protection depend on the host-parasite system and the grazing management, both of which are influenced by climate. Short-term protection may suffice for GI nematodes of cattle in regions with a restricted grazing season, such as in Europe.<sup>26</sup> In regions with continuous grazing throughout the year (eg, South America and New Zealand), the required duration of protection offered by vaccination may be similar for parasites that rapidly induce natural immunity, such as *Cooperia*, but longer protection by vaccination may be needed for parasites with a slower immune development, such as *Ostertagia* and *Fasciola*.

*F hepatica* infection levels greater than 30 to 40 flukes in cattle and 30 to 54 flukes in sheep have been associated with production losses.<sup>38–40</sup> In order to reduce fluke burdens below these threshold values, and taking into account reported fluke burdens in



different countries, vaccine efficacy against *Fasciola* should reach 50% to 80% according to Toet and colleagues.<sup>27</sup> However, it was not specified whether this reduction in fluke burden should be obtained through a direct effect of vaccination on worm viability or indirectly by reducing worm egg output in vaccinated animals. Estimating an indirect effect of reduced egg shedding on adult fluke burdens is complicated by the role of the intermediate snail host in parasite transmission. Because a snail infected with a single miracidium can produce several hundred cercariae, the snail biology has a significant impact on the outcome of vaccination.

### ***Vaccines Against Multiple Pathogens***

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In most regions, grazing ruminants are coinfectd with several pathogenic worm species; for example, *H contortus*, *T circumcincta*, and *Trichostrongylus* spp in sheep, and in cattle *O ostertagi* and *Cooperia* spp, plus others at lower levels. Multivalent vaccines, protecting against multiple GI nematodes and/or lungworms and liver fluke, could have an obvious advantage compared with single-species vaccines.<sup>2</sup> However, monovalent vaccines may be useful in situations in which a single parasite species dominates (eg, *H contortus* in warmer regions), when other parasites are controlled by alternative measures, or in regions where the risk for other parasites is low (eg, in dry regions with a low risk for liver fluke infection).<sup>2</sup> Little or no research on multispecies helminth vaccines has been conducted, to our knowledge. No cross-protection was observed against *O ostertagi* when cattle were vaccinated against *C oncophora* with a ddASP vaccine<sup>26</sup> despite the similarity of the ASP antigens of both worm species.

Helminth vaccines could also be combined with vaccines against other pathogens. However, vaccines against multiple pathogens are particularly useful when they tackle a common disease complex, such as neonatal bovine diarrhea (a combined vaccine against *E coli*, rotavirus, and coronavirus) or bovine respiratory disease (eg, vaccine against bovine respiratory syncytial virus, parainfluenza virus, and *Mannheimia haemolytica*). Parasitic gastroenteritis and lungworm disease are well-defined disease entities in grazing ruminants, and combining a GI nematode or lungworm vaccine with bacterial or viral antigens may have little advantage.<sup>1</sup>

### ***Vaccination and Other Worm Control Measures***

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In many cases, vaccination is not a stand-alone solution, especially if vaccines are targeted at single parasite species and/or confer only partial protection. However, vaccination, even if only partially effective, could become an important component of integrated worm control programs.<sup>1</sup> Anthelmintic treatment at particular time points during the vaccination schedule with the Barbervax vaccine is recommended in sheep, to cope with concurrent trichostrongylus infections or early haemonchus infections ([www.barbervax.com.au](http://www.barbervax.com.au)). Because there is a large variability of immune responses to vaccination between individual animals,<sup>14</sup> animals that respond poorly to vaccination may need to be identified and either treated or removed from the group. Likewise, herd immunity leads to reduced levels of pasture contamination that then helps protect those few animals that respond poorly. It would be an impossible task to test the huge number of possible scenarios arising from the combination of (multi-species) vaccines with other worm control measures in different management systems and climatic conditions in field vaccine trials. In contrast, helminth transmission models can be a useful tool for evaluating different scenarios in silico, and to select the most promising (combinations of) control methods for field testing.<sup>41,42</sup> Barnes and colleagues<sup>43</sup> modeled the population dynamics of *Trichostrongylus colubriformis* in sheep to predict the effect of different vaccines on worm

population dynamics in grazing lambs. They concluded that, with vaccines based on conventional antigens, substantial benefits can be obtained with a decrease of 60% in larval establishment in 80% of the flock. These simulations have been referred to in several articles to argue that it is not essential for a vaccine against GI nematodes in ruminants to obtain 100% efficacy (or even >90%) in all animals. However, these results cannot be readily extrapolated to other host-parasite systems; for example, when suppressed egg production is the main effect of vaccine-induced immunity rather than decreased larval establishment.<sup>35</sup> Turner and colleagues<sup>44</sup> developed a mathematical model to simulate the effectiveness of liver fluke vaccines under field conditions. The model output suggests that current vaccine candidates have the potential to reduce the mean total fluke burden by 43% and mean daily egg output by as much as 99% under field conditions. However, to be effective, a vaccine should protect at least 90% of the animals during the whole grazing season. It seems unlikely that this level and duration of protection can be achieved with vaccination alone, but vaccines could contribute substantially toward fasciolosis control, reducing usage of anthelmintics and thus delaying the spread of anthelmintic resistance.<sup>44</sup>

### POTENTIAL UPTAKE OF VACCINES BY END USERS

It is unlikely that the use of helminth vaccines will be imposed by policy makers, because helminth infections in livestock are considered as production diseases, without importance for public health or international trade.<sup>45</sup> Consequently, the decision to vaccinate will be the farmer's responsibility and among other things will depend on the vaccine's performance and cost-effectiveness in comparison with alternative control measures, as shown by the success of the Barbevax vaccine. Despite the need to vaccinate sheep on a regular basis and to combine vaccination with anthelmintic treatments, farmers are willing to use the vaccine because anthelmintics alone have become insufficient to control haemonchus infections in regions with high levels of anthelmintic resistance. In contrast, the lungworm vaccine is not used extensively in many countries, despite good vaccine efficacy. Practical concerns, such as a short shelf life, and the availability of anthelmintics with a persistent efficacy against *Dictyocaulus*, apparently have made the vaccine a less attractive control option.

Although ultimately it may be the farmer's decision to vaccinate, veterinarians have an important role to implement and improve vaccination strategies.<sup>46</sup> More sociopsychological studies to identify drivers of farmers' and veterinarians' decision making will be crucial to optimize uptake of novel parasite control tools, such as vaccines.<sup>47</sup>

### FUTURE PROSPECTS AND SUMMARY

Expressing recombinant vaccine antigens in the right conformation to induce a protective immune response remains an issue for many nematode vaccines. Studies on allelic variability of the target genes and on the protein conformation and secondary modifications of the antigens should help to steer the recombinant expression work and ultimately lead to the development of protective recombinant antigens. In addition, increasing knowledge on vaccine-induced immune responses will lead to optimized antigen-adjuvant combinations and improved vaccine delivery.<sup>2</sup> The sustainability of vaccines, like anthelmintics, will depend on parasite evolution, and the ability of helminths to develop resistance to vaccine-induced host responses remains an open question.<sup>41</sup> Vaccines containing multiple antigens of a single parasite species could slow down adaptation of the parasites to the vaccine, such as an experimental *Teladorsagia* vaccine in sheep that comprises multiple recombinant proteins.<sup>14,16</sup>

The effect of the level and duration of vaccine efficacy on parasite transmission and animal productivity and the combined use of vaccines and other control methods in different management systems and climate regions should be simulated using mathematical models to inform vaccine developers and regulatory authorities about possible outcome scenarios.

In parallel, consumer expectations about helminth vaccines should be investigated and drivers and inhibitors of farmers' and veterinarians' uptake of parasite vaccines should be identified to ensure that vaccines, once they are ready for commercialization, will be effectively used and incorporated into routine farm management and disease control.

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## DISCLOSURE

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