VACCINATION AGAINST PROTOZOA

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Introduction

There are few vaccines for protozoan infections in any species. Those that have been developed are summarised in Table 1. They share the common feature that all utilise living parasites which have been either attenuated *in vivo* or *in vitro* or, in the case of *Theileria parva*, are non-attenuated but in which their pathogenicity is modulated by concurrent drug treatment. Only one of these vaccines is available for sheep and this shall be discussed below.

Table 1
Vaccines for Protozoa

Babesia	Cattle	Attenuated *in vivo*
Theileria annulata	Cattle	Attenuated *in vitro*
T. parva	Cattle	Non attenuated, infection + treatment
Coccidiosis	Chicken	Attenuated *in vivo*
Toxoplasma	Sheep	Attenuated *in vivo*

Probably the two major protozoal diseases of sheep in the UK are coccidiosis and toxoplasmosis. Whilst there is no vaccine for coccidiosis I shall consider the possibilities and technical limitations for this first.

Coccidiosis

The problems in developing a vaccine for sheep coccidiosis are similar to those faced by researchers who have developed a vaccine for chicken coccidiosis and some relevant lessons can be drawn from our knowledge of the biology and immunology of the *Eimeria* of poultry. The successful poultry coccidiosis vaccine comprises live attenuated oocysts. Since immunity in *Eimeria* is species specific all seven species of *Eimeria* known to infect chickens are included in the vaccine. However, there is relatively little intra-specific heterogeneity so that with the exception of *Eimeria maxima*, single isolates of each species adequately provide protection. The vaccine lines have been attenuated by rapid passage *in vivo* to create so called precocious lines. In sheep key aspects of the biology and epidemiology of coccidiosis relevant to any vaccine development include the following; there are two main pathogenic species *E. ovinoidalis* and *E. crandallis*; peak morbidity usually occurs in lambs of about 4-8 weeks of age; and active immunity is acquired by exposure to low numbers of oocysts. There is evidence that very young lambs are less

Table 2
Coccidiosis in lambs
Immunising by Infection

	Diarrhoea	Mortality %	Wt. Gain[1] %
No immunisation	+	80	200
1 x, at birth	+	22	230
1 x weekly	-	0	240
3 x weekly	-	0	255

1. % Of weight at challenge, 63 days post-challenge (from Catchpole, Norton and Gregory, 1993)

susceptible to infection. Under seven days of age this may have a physiological basis and be due to reduced rates of oocyst excystation in the gut due to immature enzyme systems, and up a month or so of age may be mediated, in part, by passively acquired maternal antibody. It would thus be important if oocysts were used in an immunising strategy for them to be given after one week of age. This is well illustrated in data shown in Table 2 from Catchpole *et al.* (1993) where a single inoculation at birth was less effective in inducing protection than one at one week of age. On the other hand, it is advantageous if lambs are exposed to infection before maternally-derived immunity wanes. The practical inferences from this were investigated some years ago by Gregory and colleagues who found that, paradoxically lambing in very hygienic conditions tended to be more highly associated with later clinical problems than lambing in less clean situations where lambs were exposed to oocysts within the first four weeks of life.

The prospects for a coccidiosis vaccine for sheep are not good. The problems are commercial rather than technical. An attenuated live vaccine is almost certainly technically feasible but would require a substantial investment to achieve *in vivo* attenuation and would be relatively expensive to produce and quality control. There is a limited global market and the vaccine would only be applicable to sheep. The use of recombinant antigens would overcome some of the economic problems attendant in the production of a live vaccine but there has been only limited success in inducing protection in chickens against eimerian infection with defined antigens. One possible strategy might be to obtain expression of the relevant protective antigens of the pathogenic species in transfected non-pathogenic species which could potentially provide a safe live vaccine inducing protection against *E. ovinoidalis* and *E. crandallis*, but this approach is not yet proven even with poultry coccidia. Perhaps the most promising approach for the future might be the exploitation of gametocyte-associated antigens and the use of recombinants to induce maternal humoral immunity which can be passively transferred to lambs. But for the foreseeable future coccidiosis control in sheep will continue to be based on management and chemotherapy.

Toxoplasmosis

A toxoplasmosis vaccine is commercially available for use in sheep (Toxovax, Intervet). The vaccine comprises live attenuated tachyzoite stages given be parenteral inoculation. The vaccine was originally developed by researchers in New Zealand and has subsequently been developed by researchers at the

Table 3
Efficacy of Toxoplasma vaccination with S48 strain in sheep

	% viable lambs
Vaccinated (S48 m[1])	72
Vaccinated (S48 v[2])	81
Non-vaccinated	18

[1] - mouse passage
[2] - *in vitro* passage

Moredun Institute and in Intervet (Buxton, 1993). Tachyzoites are produced by *in vitro* culture and have been attenuated by multiple passage so that they do not differentiate into persisting bradyzoites which form tissue cysts. This is essential so as not to produce meat which is infective for humans. Sheep are vaccinated before pregnancy (since this is a live vaccine) and good protection is provided against foetopathy should natural challenge occur in subsequent pregnancies. The results of an efficacy study are shown in Table 3. A vaccine is particularly useful since the exposure of sheep to toxoplasma oocysts is unpredictable. Whilst foetopathy will only result should primary infection occur during gestation, oocysts may be acquired from pasture, conserved feed or contaminated bedding at any time from tupping onwards so it is extremely difficult, by management alone, to prevent exposure, and chemoprophylaxis would be required continuously throughout pregnancy. Thus a vaccine is undoubtedly the preferred and surest means of preventing the consequences of exposure. Whilst the vaccine provides good protection against abortion it does not prevent super-infection of the ewe and tissue cysts form as the result of such a natural challenge. In the absence of challenge, immunity persists for at least two years but, of course, natural exposure will re-inforce immunity. Care must be taken in administration of the vaccine to prevent self-inoculation. The problems attendant with a live vaccine such as quality control, shelf life and safety are reduced by the use of non-living vaccines. However, attempts to induce protective immunity in sheep with non-living toxoplasma antigen have met with only modest success. It is likely that non-living preparations will need to stimulate interferon gamma production since there is evidence in toxoplasmosis infection in other species that this a key mediator of protection. Whilst the use of recombinant antigens to protect against parasitic infections has met with only modest success to date there is some hope that a recombinant based vaccine for toxoplasmosis might ultimately be available for use in sheep because, since this parasitic disease affects a number of species, including humans, there is the potential for multi-species use.

In conclusion, for sheep coccidiosis there is little realistic prospect of a vaccine. The development of precocious lines or non-virulent cross-protecting species offer perhaps the most practical possibilities. For toxoplasmosis an efficacious live vaccine is commercially available and there is some prospect of a recombinant vaccine in the future.

References

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