Veterinary Parasitic Vaccines - A Current Scenario
Tarun Kumar, N. A. Tufani, Amit Prasad, Niddhi Arora, and V.S. Rajora
Department of Veterinary Medicine, College of Veterinary and Animal Sciences
G.B. Pant University of Agricultural and Technology, Pantnagar-263 145, U. S. Nagar, Uttarakhand

Abstract
Vaccinology combines disciplines of immunology, microbiology, protein chemistry, and molecular biology with practical considerations of production costs, regulatory affairs, and commercial returns. Veterinary vaccines already made enormous impacts not only on animal health, welfare, and production but also on human health. To control parasitic diseases in animals, vaccines are considered as a better alternative. However, most important barrier in the development of parasitic vaccine is incomplete understanding of the molecular and immune regulatory pathways involved in the development of immunity against parasitic diseases as well as lack of precise understanding of the host/parasite interaction.

Keywords: Parasitic vaccines, Veterinary

Introduction
The term “vaccine” derived from the Latin word “vacca,” meaning cow) was first coined by Edward Jenner. Vaccination helps in the development of acquired immunity by inoculating non-pathogenic but immunogenic components of the pathogen, or closely related organisms.

The criteria for successful Veterinary vaccine preparation vary on the animal groups under consideration. Criteria for companion animal vaccines are similar to those for human vaccines as in that the health and welfare of the individual animal are of primary concern. On the other hand in case of livestock vaccines, the main criteria are to improve overall production for the primary producers, and the cost-benefit results from vaccination. Veterinary vaccines comprise only approximately 23% of the global market for animal health products; the sector has grown consistently due to new technological advances in vaccine development, the continuous development of drug resistance by pathogens, and the emergence of new diseases (Meeusen et al., 2007). Parasitic diseases in livestock and companion animals are mainly controlled and treated by chemotherapeutic agents. With the emergence of drug resistance among different parasitic species, the situation is alarming (Sutherland and Leathwick, 2011). So safer and better parasite control methods should be searched (Hoste and Torres-Acosta, 2011). Although, a large number of vaccines against various pathogens including bacteria and virus are available in the market; but number of anti-parasitic vaccines have remained low (Gerhardt, 2006). Therefore, vaccine against parasites has to be developed and should be available in the market. This review mainly concentrates on general concepts and recent advances in Veterinary parasitic vaccines.

Protozoal Vaccines
Protozoal infections in animals cause significant production losses. They create a major obstacle in the introduction of high-productivity breeds in poorer, mainly in tropical areas around the world. Many
organisms also cause zoonotic diseases or have close relationships to human parasites, thereby increasing their significance as infection reservoirs or animal models for human diseases. While no vaccines for human protozoa are available yet, but number of veterinary vaccines are available in the market or have been produced by Agriculture/Veterinary departments for local use (Meeusen et al., 2007). Most of these vaccines are based on live organisms that stimulate an immune reaction in the hosts, mimicking natural infections. However, an increasing number of killed subunit vaccines have been developed and commercialized in recent years. The spectacular achievements in vaccines against cestodes and ticks attracting attentions in the scientific community.

A. Live protozoal parasite vaccines

Immunological mechanisms involved in protection and the stages involved in protozoal infections have mostly not been defined, so it is not surprising that most vaccines make use of the live organism itself to elicit the required protective immune response. Vaccine development for these organisms becomes tough as they display antigenic diversity in their different life cycle stages within the host as well as between different species and strains and, within the same life cycle stage, in case of hemoprotozoal parasites. Moreover protozoal parasites have a high degree of genetic complexity.

So these vaccines can be:

(i) Vaccines based on complete life cycle infections

Coccidiosis, being a major economic parasitic disease of poultry worldwide, is mainly controlled by vaccination with low doses of infective organisms. Coccidiosis in poultry is caused by the obligate intracellular protozoal parasite *Eimeria* species, which undergoes a defined number of asexual cycles of merozoite production in gut epithelial cells (three to four merogenic cycles) before the final sexual stages develop and produce the infective oocysts. As the infection is self-limiting, vaccination with small doses of oocysts induces solid protection against homologous challenge with minimal pathology. Recently developed live vaccines contain oocysts selected from naturally occurring *Eimeria* strains that produce less merogenic cycles and are therefore safer to use. But the need for simultaneous administration is needed to prevent infection of susceptible birds by vaccine-produced oocysts and species- and strain-specific immunity as suggested by Shirley et al., 2005. The commercial success of this type of vaccine lies primarily in breeder and layer flocks where anticoccidial drugs have been banned to prevent the carryover of drugs into eggs and meat (Meeusen et al., 2007).

(ii) Vaccines based on drug-abbreviated infections

East Coast fever infection used to be controlled by vaccination of cattle with pathogenic wild-type *Theileria parva* followed by drug treatment (long-acting tetracyclines). A solid protection (cell-mediated immunity) was conferred against homologous challenge, but this vaccination strategy proved to be expensive as stated by Graham et al., 2006.
(iii) Vaccines based on a truncated life cycle of parasites

*Toxoplasma gondii* infects a wide variety of hosts, including humans, and is the major cause of abortion in sheep and goats. *T. gondii* parasites when continuously passages in mice found to have lost its ability to form cysts. So incomplete S48 strain of *T. gondii* forms the basis of a commercial vaccine conferring long-lasting immunity (18 months) of susceptible ewes against *Toxoplasma*-induced abortion when administered prior to mating (Buxton and Innes, 1995).

(iv) Vaccines based on virulence-attenuated strains

Attenuated but still immunogenic piroplasms of *Babesia bovis* and *Babesia bigemina* were obtained after continuous passaging in splenectomized calves. So Live vaccines using infected blood collected from acute infections of splenectomized calves were developed in Australia several decades ago and are still used in most countries to protect against babesiosis, as reviewed by Dalgliesh *et al.*, 1981; de Waal and Combrink, 2006.

This vaccine sometimes supplemented with *A. Central* infected blood where *A. marginale* is enzootic. Many Veterinary institutes now produce frozen-blood vaccines stored in liquid nitrogen using either dimethyl sulfoxide or glycerol as the cryoprotectant so that shelf life and safety can be ensured. It is believed that a continuous exposure to natural tick infections is generally required to ensure continuous and long-lasting immunity. Tropical theileriosis in cattle used to be controlled by a live, attenuated *Theileria annulata* vaccine that has been produced by continuous *in vitro* passaging of the intracellular macroschizont stage. (Pipano and Shkap, 2000).

B. Killed or subunit protozoal parasite vaccines.

Several inactivated vaccines consisting of crude whole organisms or, more recently, defined antigenic structures are available in the animal market. But these vaccines are not as effective as live organisms but they may form the basis for the development of recombinant vaccines. *Neospora caninum* is a major cause of abortion in cattle (intermediate host). A crude *N. caninum* vaccine consisting of inactivated *N. caninum* tachyzoites with an adjuvant available in the United States to aid in the reduction of *N. caninum*-induced abortion in healthy pregnant cattle and prevent the transmission of the parasite to calves *in utero* (Romero *et al.*, 2004; Innes *et al.*, 2005). Marsh *et al.*, (2004) evaluated and proposed a vaccine that alleviates equine protozoal myeloencephalitis caused by *Sarcocystis neurona*. Vaccine consists of *in vitro* cultured merozoites, which are chemically inactivated, originally obtained from the spinal cord of a horse, and mixed with a proprietary adjuvant.

Chronic infections that are resistant to chemotherapy can be treated through vaccination, (Olson *et al.*, 2000) and it is believed that vaccine acts mainly by neutralization of parasite toxins with antibodies. *Giardia intestinalis* is an enteric parasite of many animal species and can cause severe gastrointestinal disease in young and immunocompromised individuals. GiardiaVax® a commercial vaccine has been
licensed for use in dogs and cats that significantly reduce incidence, severity, and duration of cyst shedding. The vaccine consists of a crude preparation of disrupted, axenically cultured *G. intestinalis* trophozoites (sheep isolate).

Two subunit vaccines against canine babesiosis have been developed. Both vaccines consist of soluble parasite antigens (SPA) that are released into the culture supernatant by in vitro-cultured parasites, combined with adjuvant. The first vaccine released, Pirodog®, contains SPA from *B. canis* cultures only (Moreau *et al.*, 1989) whereas recently released NobivacPiro® contains SPA from *B. Canis* and *Babesia rossi* in an attempt to broaden the strain-specific immunity. The protective effect of this vaccine seems to be based on the antibody-dependent neutralization of a soluble parasite substance (Schetters, 2005). Another subunit vaccine based on a strongly antigenic surface glycoprotein complex, fucose mannose ligand (FML) antigen, from *Leishmania donovani* with saponin as adjuvant has been developed against canine visceral leishmaniasis, in Brazil. Vaccine found to have 76 to 80% efficacy against both homologous and heterologous challenge with *L. chagasi* and to last for at least 3.5 years (da Silva *et al.*, 2000). The vaccine may also havea therapeutic effect on infected dogs.

A killed subunit vaccine has been developed against coccidiosis in poultry by ABIC Veterinary Products, Israel (Wallach *et al.*, 1995). The vaccine targets the final sexual, macrogametocyte stages that develop to form the disease transmitting oocysts. This vaccine strategy works under the principle that it will allow immunity against the asexual stages to be generated by natural infections while reducing oocyst shedding and parasite transmission. Moreover protective immunoglobulins may be transferred into the egg yolk and subsequently the hatchlings by immunizing laying hens, rather than the chicks so this considerably reduces the number of vaccinations and animal handling. It is expensive to produce this type of vaccine as it consists of affinity-purified native gametocyte antigens derived from infected chickens, and is still a fairly complex preparation (Belli *et al.*, 2002). To identify the protective components so to develop a recombinant vaccine, three major components of affinity-purified native gametocyte antigens have recently been cloned and characterized (Belli *et al.*, 2004).

**Helminth and Ectoparasite Vaccines**

Foster and Elsheikha (2012) reviewed advances in the immune response to selected helminths of animal health significance, and subsequent vaccine potential. Some important topics like helminths interaction with the host immune system were assessed to better understand the pathogenesis of diseases caused by helminths.

Mainly there are three different families of helminths i.e nematodes (roundworms), trematodes (flatworms), and cestodes (tapeworms), that infect both animals and humans. Only one worm vaccine i.e. against cattle lung nematode *Dictyocaulus viviparous* is available in the market and used in Europe. The vaccine contains irradiated L3-larvae that do not mature to adult worms (Ploeger, 2002). A similar
approach was used to develop a vaccine against the canine intestinal nematode *Ancylostoma caninum* (Miller, 1978) but it was observed that irradiation-attenuated larval vaccines developed against gastrointestinal nematodes did not protect young, susceptible stock against infection and were, therefore, never commercialized (Knox, 2000). Moreover larvae must be harvested from the manure of infected animals so these vaccines are difficult to produce too. The increasing drug resistance of gastrointestinal nematodes has renewed intense interest in developing vaccines for these important veterinary pathogens. Commercial or field application of anticestode vaccines is still in progress. Effective recombinant vaccines were developed against the cestodes *Taenia ovis*, *T. saginata*, *T. solium* and *Echinococcus granulosus*. These vaccines are based on antigens of the parasite stage that adheres to the gut wall. When used for vaccination, these antigens induce immune responses that interfere with successful attachment. The vaccine against the cestode *T. ovis* has been registered in Australia and New Zealand, but has not been marketed (Lightowlers *et al*., 2003).

Vaccine development against trematode species like liver flukes is hindered as they do not seem to induce immunity in their natural ruminant hosts, even after repeated infections. New approaches need to be developed to produce vaccines against these parasites.

Ectoparasitic arthropods would seem to be the ultimate challenge in vaccine development, as they not only are large and complex but also spend most of their life outside or on the surface of the host. Vaccine against the cattle tick, *Boophilus microplus*, is a recombinant vaccine based on a protein (Bm86) found in the tick at the surface of the gut wall. It was first introduced commercially in Australia in 1994 (TickGUARD®; Fort Dodge Australia). This vaccine is unique in that it is not based on natural antigens recognized by the immune system during infection but takes advantage of the ferocious blood-feeding habits of the tick. Vaccination stimulates the production of high antibody levels in cattle against a tick gut membrane-bound protein, Bm86, using a recombinant protein in a potent adjuvant. These antibodies bind to the tick’s gut surface when taking a blood meal, causing the rupture of the gut wall and tick death (Knox and Smith, 2001). The vaccine induces significant levels of protection against tick infestation and, in some cases, against tick-borne diseases. However antibody levels are not boosted by infection and need to be maintained at high levels by repeated immunization. Use of vaccine in conjunction with drug administration, limits its practical and commercial use. Moreover the presence of a tick immunoglobulin excretion system hampers the effectiveness of this vaccine approach in other ticks (Nuttall *et al*., 2006).

Certain more barriers in parasitic vaccine development include that they have highly complex life cycles and there is a general lack of precise understanding of the host/parasite interaction.

Efforts towards vaccine development should be pursued intensively. Many vaccines may find their greatest and most immediate application in integrated control strategies. The synergies offered by a
combination of vaccines and parasiticides should be thoroughly explored, as this approach may lead to a substantial reduction in the use of parasiticides.

References


