Vaccines in Control of Coccidiosis

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Abstract: Worldwide, the poultry industry spends a significant amount of money in the prevention and treatment of several diseases. One of those diseases, avian coccidiosis, is caused by several species of the protozoan parasite *Eimeria*. This parasite invades epithelial tissues of the intestine, causing severe damage in birds and as a result, significant economic losses. The main problem with *Eimeria* infections is that they are caused by more than one species that attack different regions of the intestine. The use of several drugs, alone or in combination, has proven to be an effective alternative in the struggle against avian coccidiosis. However, the emergence of drug resistant strains, especially after a prolonged use of a drug, is a real problem. Thus, vaccines are the only preventative method. Conventional disease control strategies depend on vaccination or immunization. *Eimeria* infection or its developmental stages promotes antibody and cell-mediated immune responses. The purpose of this review is to present approaches for the replacement of coccidiost at application in chickens through improvements in poultry house management, research in vaccine developments, and application of holistic natural products for the prevention of the economic losses resulting from coccidiosis.

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Introduction

Coccidiosis is a major parasitic disease affecting the poultry industry worldwide. It is initiated by the exposure of chicken to a sufficient dose of coccidia that can produce clinical signs and intestinal injuries. *Eimeria* is a genus of Apicomplexan parasites that includes various species responsible for the development of coccidiosis. All species of *Eimeria* invade the lining of the intestine; however, seven species are considered of economic importance, due to their proven pathogenicity *namely, Eimeria acervulina*, *E. brunetti, E. maxima, E. mitis, E. necatrix, E. praecox,* and *E. tenella.* The significant role that *Eimeriahagani* and *E. mivati* have in coccidiosis is still not well-established **(Tsuji *et al.*, 1997; Vrba *et al.*, 2011).** The simultaneous field infection with two or more species of *Eimeria* is common, in which each species causes an independent and recognizable intestinal injury, apart from the other species. Coccidia are transmitted to the host through oral fecal ingestion. The development of the parasite *Eimeria* includes both an exogenous phase, where oocysts sporulation takes place in the environment to become infective, and an endogenous phase, where asexual and sexual stages of development occur, thus leading to the lysis of the host intestinal tissue **(Conway and Mckenzie, 2007).** The common outbreaks by coccidiosis in chicken required a preventive interception through the past decades by the application of coccidiostats in their feed. A continuous in-feed low concentration of anticoccidial drugs to control *Eimeria* was reported early in the 1930s and mid-20thcentury **(Grumbles *et al.*, 1948; Levine, 1939).** These researchers showed for the first time that it was possible to control coccidiosis by the continuous inclusion of a low level of a drug in the feed of chickens (prophylaxis or prevention). However, the use of suboptimal levels of the anticoccidial drugs may increase the probability of selecting drug-resistant strains **(Chapman, 1984).** Shortly after introduction of sulphaquinoxaline and nitrofurazone, resistance had been reported **(Cuckler and Malanga, 1955;).** Since that time, many reports concerning anticoccidial drugs resistance were reported **(Chapman, 1997)**. It is therefore possible that in medicated birds adequate parasite multiplication may occur, promoting the development of immunity, which allowed producers to increase the duration of the withdrawal period (less cost or less food residues), at the risk, however, of increased susceptibility to coccidiosis and outbreaks (**McDougald & Reid, 1971)**. From a practical point of view, it is important not to withdraw anticoccidial drugs ahead of time, since birds may not have developed solid immunity. Solid immunity in medicated birds did not develop until birds were6 to7 weeks of age **(Chapman, 1999a, b).**

Poultry House Management In Control Of Coccidiosis

Eimeria has a high reproductive ability, thus practically it would be very difficult to keep the environment around the chickens free from these organisms. The global control of chicken coccidial infections in the poultry industry is becoming harder due to the high stocking density of the flocks. Documented research indicated that the enhanced risks of coccidiosis are environmental and management factors, as well as hygienic practices that are exercised on the farm, including visitors, presence of feeders and drinking systems that are difficult to clean, and the high probability of carryover of this parasite from previous infected flocks **(Graat *et al.* 1998; Belli *et al.* 2006).** Many poultry producers opted to remove the used litter, expose the farm house to fresh air for a period of 2-3weeks, and then add the new fresh bedding beforeintroducing the new flock. Other producers have reliedon a thorough cleaning and disinfection of the poultryhouse and used equipment before the introduction of a new flock. The latter is a husbandry practice that is has been increasingly adopted, due to the decreasing efficacy of anti-coccidial drugs and the increasing use of live vaccines **(Allen and Fetterer, 2002)**. The degree of sporulation is determined by environmental factors like temperature, humidity and aeration. Ambient temperature of 25o C and relative humidity greater than 60% will favor the oocysts porulation and viability (**Razmiand Kalideri, 2000).** The percentage of chicken coccidial sporulation is higher in dry litter than in wet litter, which is most likely due to the buildup of bacteria, ammonia and the poor aeration in wet litter, resulting in loss of oocyst viability **(Waldenstedt *et al.*, 2001).** However, increasing litter humidity is not recommended in broiler production as it causes skin burns, footpad lesions and consequent lameness. In addition, proper ventilation is recommended for better performance of the bird, but it provides a drier litter that favors sporulation. Reducing bird density seems to be the proper management practice for reducing oocyst accumulation in the litter, and lowering the chances of occurrence of an outbreak of clinical coccidiosis **(Chapman *et al.*, 2002).**

Vaccines in Control of Coccidiosis

Although the concept of vaccination using live oocysts was conceived by **Johnson (1927),** it was Edgar who first turned this into a commercial reality **(Edgar, 1956; see Williams, 2002).** His vaccine (Coccivac), which consists of a mixture of oocysts of important species to be administered at a low dose to birds, was introduced in 1952 and is still widely employed today in various forms. Technical information on the efficacy of this vaccine was never reported in the scientific literature.

A key to the recent success of vaccination with live oocysts, especially in broilers, is the realization that protective immune responses can be produced following immunization with low doses of oocysts in day old chicks **(Long et al., 1986).** Also the development of practical means of delivery, such as the use of spray cabinets in the hatchery, thus avoiding the need to vaccinate birds in the poultry house, has facilitated the adoption of vaccination with live oocysts as a practical means of control. The induction of solid immunity can be achieved by repeated inoculation of birds with low numbers of oocysts **(Joyner and Norton, 1973). Davis et al., (1986)** proposed that such a "trickle" exposure could be achieved by encapsulating oocysts in gel beads that could be fed to chickens, a concept that has recently been revived (**Jenkins et al., 2012). Jeffers (1986)** suggested that alternating cycles of immunization an chemotherapy might provide effective long-term control of coccidiosis, and **Chapman (1994b)** subsequently demonstrated that sensitivity to monensi could be restored following use of a live vaccinein commercial broiler production. Similar observations were made for the synthetic drug diclazuril **(Mathis and Broussard, 2006).** Various programs involving alternation of vaccination with the use of drugs have therefore been proposed with the object of achieving sustainable coccidios is control **(Chapman, 2000).** The identification of gametocyte antigens from *E.maxima* by Wallach and colleagues has led to a different approach to vaccination in which hens are injected with2 proteins (gam56 and gam82) derived from the wall forming bodies of macrogamonts **(Wallach et al., 1989, 1992).** The resultant IgY antibodies are transferred via egg yolk to chicks and confer protection against *E.maxima* and other species early in life. A vaccine based on this principle, the first subunit vaccine for an apicompl exanparasite, is now used commercially in some countries drugs **(Reid, 1970),** The developed vaccines for coccidiosis were mostly live, divided into two categories namely, no attenuated and attenuated vaccines. Other minor trends in the development of coccidial vaccines include subunit, recombinant, and DNA-based vaccines. It is of paramount importance to withdraw the anticoccidial drug from the chicken feed when the administered live vaccine contains live strains that are susceptible to that drug. It is worth noting that live vaccines usually contain strains that are sensitive to commonly used anticoccidial drugs **(Peek and Landman, 2006).** Live vaccines can modulate the field strains of *Eimeria* by respective reduction of their resistance to anticoccidial drugs, and by lowering of their virulence through exchange of genetic information between drug–sensitive attenuated strains in the vaccine and the wild-type strains in the local population of the farm **(Williams, 1998).** The use of live vaccines for broiler chickens was restrictive for a period of 50 years. Their

primary use was for layers and breeders **(Shirley *et al*., 1995).** The use of live vaccines in broiler flocks increased significantly during the last decade, mainly due to the improvement of management practices around the globe **(Williams, 2002).** Live vaccines contain strains that are either attenuated (precocious strains) or non attenuated (virulent, wild-type strains). An overview of these available commercial registered live vaccines is compiled by **William (2002)** and **Peek and Landman (2006)** Live commercial vaccines are divided into non-attenuated and attenuated categories Attenuated vaccines develop faster than the non attenuated vaccines due to their short life cycles; lower, **(Shirley *et al*., 2005).** the consistent larger outputs in oocysts of parent compared to precocious strains of different species of *Eimeria*. The crowding effect in nonattenuated lines, in the presence of limited epithelial cells and efficient cell mediated immunity, will result in reduced reproduction of oocysts, especially when chickens are exposed to high doses. Consequently, the lower fecundity of the attenuated lines is better for parasite reproduction, leading to enhanced immunity development. The marked immunological diversity found among *E. maxima* species raises concerns about the efficacy of the developed vaccines against it. Vaccinating against one strain of *E. maxima* may not protect against the other *E. maxima* strains present in the field. Immunological relevance has been demonstrated experimentally with cross protection between strains ranging from 10 to 70 %, based on the oocyst output and lesion score **(Smith *et al*., 2002).** The inclusion of two strains of *Eimeria maxima*, representing extreme immunological diversity, seems indispensable **(Shirley and Bellatti, 1988).**

Subunit and recombinant vaccines

Subunit vaccines are engineered proteins derived from the virulent *Eimeria* parasite. The identification of specific antigens in the *Eimeria* spp., at different stages of its life cycle that are capable of inducing protective immunity, is a necessary step in development of subunit vaccines. Recombinant proteins of both the protozoan surface and internal antigens were identified as candidates for such vaccines. The most widely tested anticoccidial subunit vaccine candidates are listed in **Blake and Tomley (2014)**. The focus on surface proteins included mainly the invasive stages of *Eimeria,* namely sporozoites, merozoites, and gametocytes. These recombinant proteins induced an acceptable level of humoral and CMI immunities, that resulted until the present time in one commercial registered product, CoxAbic®, documented by **Wallach (1997)**. The CoxAbic® is an oil emulsion vaccine inducing maternally derived antibodies aimed at protecting the broiler progeny **(Finger and Michael, 2005; Ziomko *et al*., 2005)**. This is the only available recombinant commercial coccidiosis vaccine that transmits passive immunity through the yolk of hatching eggs to the progeny. The acquired immunity in the chicken breeders is developed against purified gametocyte antigens 230kDa, 82KDa, and 56KDa of *E. maxima* that are present in this recombinant vaccine **(Wallach, 1997)**. The immunization of the breeders by the mentioned gametocyte antigens is proven to protect their offspring from challenges with *E. acervulina*, *E. maxima*, and *E. tenella*, reducing oocyst output by 60-80%, in comparison to similarly challenged offspring produced by breeders that were deprived of vaccination **(Wallach, 1997).** A relevant limiting factor in the development of recombinant vaccines for protection against coccidiosis is the lack of information related to the nature of antigens responsible for the potent protective immunity against field strains. There is a great need for further investigation on the field *Eimeria* strains host interaction, both at the cellular and molecular level, with the hope of the discovery of appropriate recombinant vaccines that can protect against the diversified prevalent field strains. The *E. tenella* genome project may be helpful in identifying the protective antigens in this parasite and their interaction with the host immune system **(Shirley *et al*., 2007).**

DNA-based vaccines

The DNA-based vaccines that could be developed in the DNA-based vaccines that could be developed in the future to protect against coccidiosis will adopt the technology of including in the product specific genes that encode for protective immunogenic proteins of the *Eimeria*. These genes are administered in conjunction with promoters and enhancers. In addition, vectors are ligated to these genes to ensure their penetration to inside the chicken cells, resulting in efficient translation of the protective antigenic proteins **(Dallouland Lillehoj, 2006).**

Advantages of live Eimeria spp vaccines

Live *Eimeria* vaccines are a practical and important alternative to the exclusive use of coccidiostats that may leave residues in poultry products for human consumption. A number of studies indicated that *Eimeria* vaccines provide a protection level against coccidiosis in broilers similar to that obtained by anticoccidial programs; actually, the vaccine administration through a gel at 1 day of age proved to ensure a synchronous exposure and homogeneous protection among the birds (**Jenkins *et al*., 2012**). The use of live vaccines leads to a replacement of the drug resistant strains of coccidia in the broiler house with drug-susceptible vaccine strains. This increases the efficacy of anticoccidial drugs that are used in rotation programs with vaccines **(Williams, 1998).** In addition, live vaccines allow the

gradual buildup of solid immunity, and provide protection against subsequent coccidial challenges, associated with an acceptable safety and minimal tissue damage, especially with the use of attenuated vaccines **(Williams, 1994)**.

Disadvantages of *Eimeria*s pp. vaccines

The produced oocysts of *Eimeria* spp. that are included in live vaccines have a known tendency of losing their infectivity to the host with prolonged storage periods, thus compromising their efficacy in inducing an acquired immunity in the birds **(Jeston *et al*., 2002).** Moreover, vaccine oocyst production is costly, since their propagation is restricted to living chickens, and no cell line is yet available for their multiplication.

In addition, the antigenicity of the coccidial strain scan vary according to geographical locations. Thus, it is important to characterize at the molecular level the local populations of the coccidial parasite, and to determine the ability of the available live vaccines to protect against the prevalent field strains **(Danforth, 1998)**. Moreover, there is a risk of introducing undesirable *Eimeria* species present in the live vaccines into the farm environment. This requires the tailoring of *Eimeria* spp. vaccines that contain oocysts of the species that are matching in its antigenicity to the ones that are prevalent in a certain geographical area. The live vaccines carry the risk of causing economic losses when administered to immune-suppressed chickens **(Anderson, 1977).** The improper administration of the live *Eimeria* spp. vaccines may result in asynchronous exposure to the birds, with significant variation in the number of ingested oocysts, resulting in unacceptable homogeneity of their immunities, and a possibility of coccidiosis outbreak in birds with low immune responses to protective antigens of *Eimeria* **(Chapman *et al*., 2002).**

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