

What can we learn from *in ovo* embryo vaccination?

Introduction

In ovo (in the egg) route of vaccine administration was first shown to be safe and effective in a 1982 publication for Marek's disease.¹ Shortly after in 1992, *in ovo* vaccination becomes fully automated and has been commercially in wide use for over 25 years² for a number of poultry vaccines including Marek's disease, Infectious bursal disease, Newcastle disease, Avian influenza, Coccidiosis, and *Mycoplasma gallisepticum*.^{2,3} Experimentally, an increasing number of publications have shown the safe and efficacious applicability of the route towards the administration of probiotics, growth promoters, hormones, or nutrients.²⁻⁴ Administration of biologics through the automated delivery system occurs around day 18±0.5 of embryonic development (ED) through a dual needle: a piercing needle that pierce the shell over the air cell and an injection needle that goes through the piercing needle to a depth of about 2.5cm delivering the biologics into the amniotic cavity.^{2,3} It takes 21 days for complete chick embryonic development. *In ovo* vaccination offers many advantages over conventional day-of-age vaccination. One of these advantages that is relevant to the topic raised here is its ability to stimulate an earlier innate and adaptive immune responses as compared with the conventional post-hatch (day 1 of age) vaccination.⁵ These earlier immune responses included the activation of certain immune cells or the differential expression and release of certain cytokines.⁶⁻⁸

In chickens, fertilization of the ovulated ovum takes place within three hours of ovulation (as early as 15 minutes of ovulation) within the infundibulum, the first segment of the female reproductive tract. Fertilization is followed by cell division (or cleavage) of the fertilized egg. Embryonic cell division continues throughout the descent of the fertilized egg through the oviduct under body temperature of 40°C. By the time of oviposition, the embryo (now forming a layer of cells called blastoderm) has about 50,000 cells (blastula stage) where the blastoderm remains at this stage due to the colder temperature (commercially is kept at 21-22°C) outside the female reproductive tract. Once the blastoderm is placed under the influence of a higher temperature, be it natural or artificial incubation, the blastoderm is brought into action, thus continuing embryonic development. The blastoderm enters the next phase of embryonic development differentiating its cells into three germ layers (ectoderm, mesoderm, and endoderm) in a process called gastrulation where pluripotent stem cells migrate and make a decision that will determine their future fate. Of these stem cells, hematopoietic stem cells (HSC) become committed prior to colonizing hematopoietic organs. They originally emerge from the yolk sac (erythroid and a rare myeloid lineages), and the early aorta and the allantois (lineages with multipotent differentiation capacity).⁹⁻¹¹ These cells later-on will populate primary immune organs for maturation and then leave to the peripheral including secondary lymphoid organs as functional immunocytes.

In ovo introductions of biologics were approached from the fact that chickens have developed certain immunologic functions before hatching. Thus, it is evident that the immune system of chick embryo is functional, albeit at a late stage of ED (last 3-4 days of ED). Obviously, there is an opportunity to modulate the component(s) of the chick immune system. Modulation could start very early during the first few days of ED. For instance, there is a potential to modulate the fate of HSC by administering modulators at very early stage of chick ED, possibly around day ED4. The effects of such modulator on

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cell phenotype or its ability to express certain cytokines or even new ones is very possible, which may lead to fundamental changes in the field of immunology. Hormones (and non-replicating microorganisms) seem to be potential modulators since they are natural and were shown to play a role in the function of a mature immune system.¹²⁻¹⁵ Additionally, egg yolk, and to a certain degree egg white, contain various hormones including steroid and thyroid hormones.¹⁶ Another target day for *in ovo* administration of modulators could be around day ED9 which would potentiate the activity of immune components. Thus, *in ovo* vaccinations offer opportunities to new discoveries; immunology is a candidate field.

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Conflict of interest

The author declares there is no conflict of interest.

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