EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

15 March 2010
EMA/CVMP/IWP/439467/2007
Committee for medicinal products for veterinary use (CVMP)

Reflection paper on the demonstration of a possible impact of maternally derived antibodies on vaccine efficacy in young animals

Draft agreed by Immunologicals Working Party	January 2009
Adoption by CVMP for release for consultation	12 March 2009
End of consultation (deadline for comments)	30 September 2009
Agreed by Immunologicals Working Party	February 2010
Adoption by CVMP	10 March 2010

Keywords	Maternally acquired immunity, maternally derived antibodies (MDAs), young animals, vaccine interference, vaccine efficacy

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1. Introduction

Protection against infectious diseases is normally provided in neonatal and young animals by passive maternally acquired immunity and/or by active immunity induced by early vaccination. In mammals, early protection results from uptake of circulating maternal antibodies via the colostrum shortly after birth but can also continue via the milk during the period of lactation (the so-called lactogenic immunity). In some mammalian species, a smaller or larger portion of maternal antibodies is transferred to the fetus via the placenta. In avian species, maternal antibodies are transferred via the egg yolk towards the progeny. In general, the extent and duration of the protection of the offspring or progeny offered by maternally acquired immunity, in which maternally derived antibodies (MDAs) play a major role, are proportional to the amounts received from the mother.

Active immunization of embryos, neonates and young animals can be obtained with vaccines which can be safely administered *in ovo*, soon or shortly after birth and can provide satisfactory levels of efficacy after one or more administrations, depending on the level of MDAs and the potential of a vaccine to immunize and confer subsequent protection despite the presence of MDA. This is a particularly challenging task as the relative immaturity of the immune system in early life of animals and the potential interference of passively acquired MDAs may hamper the formation of active immunity, thus leading to failure of response to vaccination. The age, at which the young animal can be optimally vaccinated without experiencing any negative impact on vaccine efficacy is difficult to estimate .Determining the optimal age and schedule of vaccination is, therefore, of crucial importance in order to balance benefits and risks inherent with the use of vaccines in young animals.

The aim of the present reflection paper is to give guidance on how to demonstrate to which extent MDAs may have an impact on the efficacy of vaccines when administered to animals at an age at which maternally acquired immunity is still present.

2. Scope

This reflection paper applies to all veterinary vaccines submitted for authorisation via centralised, decentralised, mutual recognition and national procedures, unless justified. This reflection paper gives an example of data that should be provided when a vaccine is intended to be used in young animals which potentially have MDAs. Alternative approaches or protocols may be appropriate in some situations. If the applicant can demonstrate that the interference of MDAs is not a problem with regard to the efficacy of the vaccination (e.g animals to be vaccinated have reached an age at which MDAs are no longer present), this reflection paper is not relevant.

3. Legal basis

This reflection paper has to be read in conjunction with Part 4 Efficacy of Title II of the Annex I to Directive 2001/82/EC as amended. In particular, general provisions of part 4 clearly require that the influence of passively acquired and maternally derived antibodies on the efficacy of a vaccine shall be adequately evaluated, if appropriate.

4. General requirements

If vaccination is recommended in animals at an age at which maternally acquired immunity may still be present and may interfere with active immunity development, studies to determine whether or not such interference occurs should be performed.

The degree, persistence, and natural decay of MDAs may vary considerably depending on factors such as animal species, immune status of the mother, quantity and time of colostrum uptake by the neonate, rate of catabolisation etc. The level of antibodies in the dams in the general population may be highly variable, resulting in variable, low or high levels of MDA in the progeny. The antibody levels could be variable, for example, when the dams may be vaccinated at a time before they are pregnant and when there is a relatively low incidence of the relevant disease in the environment. The levels may be low, for example, when there is only a low or short-lived level of antibodies induced by a vaccine or disease agent. High levels could be expected, for example, when there is routine vaccination of dams in pregnancy with a highly immunogenic vaccine. Consequently, the age at which MDAs no longer interfere with efficient activation of the young animal's immune system upon vaccination will vary considerably. Factors including the type of vaccine and the route of administration also have to be considered when evaluating the impact of passive MDAs on the development of an active immune response in the vaccinated animals.

5. Possible impact of MDAs on vaccine efficacy

Depending on the nature and the properties of the vaccine (e.g. dose and strain of live vaccines) and/or on specific circumstances related e.g. to the vaccination programme or method of administration (such as: *in ovo* vaccination, vaccination against ubiquitous pathogens, etc.), laboratory and/or field studies are necessary to demonstrate the efficacy of a vaccine administered in the presence of passive MDAs.

As a matter of principle, the extent and duration of passively acquired immunity should be determined but such data can generally be gathered from scientific publications, from field trials or from the populations on the premises where animals are selected for performing MDA interference studies.

To verify the presence or absence of interference by MDAs on the vaccine take and thus with the efficacy of the vaccination, a study similar to that described below, but modified as necessary to take account of the particular circumstances, can be performed.

Three groups of animals at the minimum age recommended for vaccination are used. One group (group 1) contains animals without MDAs. The two other groups (groups 2 and 3) consist of animals having MDAs. The level of MDAs is measured in each animal by using a validated laboratory test relevant for detecting such antibodies. The MDA titre found should be representative of the titre of animals of the minimum age to be vaccinated under field circumstances. Possible reference made to varying degrees (low, medium, high) of MDAs should be justified.

The recommended vaccination schedule should be applied to two groups of animals, one with representative MDA titres (group 2) and one without MDAs (group 1). The third group of animals (group 3) with MDAs should not be vaccinated and should be followed for decay of MDAs.

For live vaccines, batches containing the minimum titre or potency shall be used unless justified. For other products, batches containing the minimum active content shall be used unless otherwise justified.

The follow up of the study depends on whether or not an established parameter related to protection is available (see also table below):

a) If the applicant has previously demonstrated that there is a direct correlation between a selected parameter (e.g. antibody titre) and protection against disease, a follow up of this parameter will be adequate and group 1 is not needed.

At the age when, in the group of animals with MDAs and not vaccinated (group 3), MDAs have become low to undetectable, the vaccination in the group vaccinated in the presence of MDAs should have induced a satisfactory value for the protection related parameter. It is possible, if justified, to investigate the effect of MDAs on vaccine induced protection under field conditions, in which case the non vaccinated group (group 3), intended to follow the decay of MDAs, would also serve to exclude that field infections have occurred.

b) If there is no direct correlation between an established parameter and protection, then a challenge experiment is needed.

Challenge should be performed at the age when MDAs have disappeared or have reached low levels in group 3 that has not been vaccinated. One or more parameters to demonstrate protection from challenge should be evaluated (e.g. clinical, pathological, virological, bacteriological criteria) and it should be shown that the efficacy of the vaccine in animals vaccinated in the presence of MDAs is, notwithstanding normal biological variation, similar to that obtained in animals of the same age but vaccinated in the absence of MDAs.

If the results of the study indicate that the MDAs interfere with vaccine efficacy, this point should be indicated in the SPC and the applicant should define the schedule of vaccination that will ensure protection of animals vaccinated in the presence of MDAs, under the circumstances claimed in the SPC and leaflet text.

Table 1. Table 1: Summary of the protocol

Group	**MDA status**	**Age**	**Vaccination**	**Serological follow up of MDA**	**Challenge**	**Interpretation of results if MDAs do not interfere with vaccination efficacy**
1*	MDA -	Minimum	yes	yes	Yes if no use can be made of a protection related parameter	If correlation exists between a selected parameter and protection, the values obtained in group 2 should be protective. If no such correlation exists, protection upon challenge in group 2 should, notwithstanding normal biological variation, be similar to that observed in group 1
2	MDA +	Minimum	yes	yes		
3	MDA +	Minimum	no	yes		Group 3 = control group. which allows : -to define the time of endpoint for examining the protection related parameter in group 2 or the time of challenge in all the groups, -to check the absence of intercurrent infection, -to validate the challenge.

* This group can be omitted in the case that the effect of MDA on vaccine induced protection is investigated on the basis of a protection-related parameter.