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Combination Veterinary Vaccines: Choices and Chaos

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Introduction

Vaccination is one part of an effective health programme as it helps to prevent disease and is more cost-effective than treating sick animals. So, the main objective of livestock vaccines is to improve overall livestock production for the primary producers, and the cost-benefit resulting from vaccination is the bottom line for this industry. Apart from improving animal health and productivity, veterinary vaccines have a significant impact on public health through reduction in the use of veterinary pharmaceuticals and their residues in the human food chain. Further, to control new emerging diseases such as IBR, BVD & Bluetongue and to keep the existing diseases under control, the number of vaccination shots increasing year to year. This increasing complexity of the immunization schedule has resulted in the need for combination vaccines.

What are "Combination" and "Simultaneous" vaccines?

A combination vaccine is the mixture of two separate vaccines mixed, prior to administration or vaccines that are separately manufactured but combined into one product during the final packaging stages. Simultaneous vaccination is when more than one vaccine shot is administered at the same time, usually on two places. An example of simultaneous vaccination might be administering DPT+IPV in humans and BVD+IBR in animals.

Advantages of combination vaccines

- Reduces the cost of packing in separate containers.
- Reduces the cost of stocking.

- Fewer vaccination programmes release veterinarians to cope with other healthcare needs.
- Facilitating the addiction of new vaccines into immunization programmes.
- Delivery logistics are simplified.
- Farmer compliance is increased, leading to simplified record keeping and surveillance activities.
- Reduces the environmental pollution with disposables and cotton during the vaccination programmes.

Hence, combination vaccines are critical to the success of vaccination programmes but each new combination must be studied to ensure comparable safety and immunogenicity of the individual components.

Disadvantages

- Antigenic compatibility with other antigens or immunological interference: potential competition among antigenic components and epitopic supression, which may reduce the immunogenic response.
- Volume of the vaccine that can be given: so antigens have to be concentrated.
- Use of inactivants and adjuvants in the combination. Increase antigenic/adjuvant ratio there by reduces the adjuvant efficiency.
- Antigenic stability in formulation may be reduced.
- Each component antigen has to be indicated at the time in the immunization schedule.
- The theoretical potential for side effects increases with combination vaccines due to increased endotoxin or toxoid load or simply as an additive effect of the individual component's side effect.
- Difficulty in assessing severe adverse reactions due to complexity of the formulation of combination vaccines.
- If only combination vaccines are available in the market, there may be unnecessary administration of a vaccine component with lifelong immunity along with a component with short lived immunity.

General principles of combination vaccines

- Ideal combination vaccines re a safe and effective as each of their single component.
- They should be easily stored and easy to administer.
- Combination vaccines facilitate adherence to recommended immunization schedules by reducing the number of immunization campaigns.
- Combination products should potentially decrease the amount of adjuvants and preservatives when compared with multiple, single-antigen products.

Factors to be considered while combining vaccines

Basing on the principles of combination vaccine and disadvantages the following parameters must be considered while combining the vaccines.

- Current immunization schedule; Combination vaccines should fit the currently recommended schedule.
- Compatibility of components: Any of the combined vaccine component i.e not only the antigens, but other chemical components should not have any effect on any of their counterparts.
- Availability of antigens for targeted diseases.
- Safety.
- Efficacy and immunogenicity.
- Route of delivery.
- Shelf life of individual antigens.

The possibility and convenience of each combination of antigens, especially when they differ in an immunological respect, must be theoretically grounded and checked by biological experiments taking into account the characteristics of the infective agents against which the active immunization is intended, the pathogenesis of these infections and immunogenesis they provoke.

Strategies for development of combination vaccines

- Immunologic interference between antigens
- Formulation of antigens
- Physical/chemical interactions between Inactivating agents, Adjuvants, Preservatives and Stabilizers.

Combining multiple components changes the sample matrix, therefore, formulation of vaccine is a very critical & crucial step in developing the combination vaccines either with multiple strains or organisms.

For example, the live IBR marker vaccine has an immunosuppressive effect over the inactivated BVD vaccine, when administered in combination, where as no such negative effect was seen when the two vaccines were applied simultaneously. However, the same vaccine did not interfere with the immune response induced by an inactivated respiratory combination vaccine or an inactivated vaccine against bluetongue. Hence, vaccines cannot be randomly combined.

Evaluation & Licensure Issues

Each combination vaccine must be evaluated to meet minimum standards for safety and effectiveness. As per Indian Pharmacopeia, if no monograph is included for a mixed vaccine, it complies with the requirement for the individual component vaccines. Any label claim concerning protection against clinical disease has to be supported by study data, which requires suitable disease models. In the development of new combination products, acceptable endpoints and immunization goals should be clearly defined. In general, any new vaccine has to be evaluated for sterility, safety, potency, immunity and stability.

In-vitro tests for combination vaccines have been limited by unanticipated interactions between vaccine components, adjuvants. Even when a correlation is established with some invitro potency tests, they may lose their predictive power for protective efficacy when applied to combination vaccines. For example, in Africa, cattle were inoculated with a dual preparation of RP and CBPP (*M. mycoides*) vaccine. There was a very good serological response. However, after subcutaneous challenge, the dual vaccinated groups were not protected against CBPP. This would indicate that the RP virus component was interfered with te ability of the *M. mycoides* component to induce a fully effective immune response. Hence, challenge is ultimate test to know the vaccine efficacy or potency, not only for combination vaccines, but also for monovalent vaccines.

Types of Combination vaccines

1. Genetically engineered combined vaccines: Recently, genetic engineering has been applied to design new, improved vaccines. These are the future vaccines because the marker vaccine concept is universally accepted and used. They are of two types:

   a. Selecting a non-infectious organism, that satisfies other parameters for eliciting immunogenicity and inserting the DNA of more than one pathogen into it.

   Adenovirus vectors are highly efficient for gene transfer and induce humoral, mucosal and cellular immune responses to antigens encoded by inserted foreign genes. Thus, adenoviruses have become a vector of choice for delivery and expression of foreign proteins for vaccination.

   The canarypox virus vector system has been used as a platform for a range of veterinary vaccines including WNV, canine distemper virus, feline leukemia virus, rabies virus and equine influenza virus.

   b. The use of an attenuated viral pathogen as the vector, with the aimof inducing protection against two diseases.

Vaxxitek: Turkey herpesvirus (HVT) is nonpathogenic in chickens but confers cross-protection against MDV and has traditionally been used as a live vaccine against MD. The new vaccine is based on a recombinant parent HVT virus expressing the VP2 gene of IBD.

2. **Combination of conventional live freeze-dried or inactivated vaccines.**
3. **Live+ Inactivated vaccines:** the inactivated vaccine in the diluent to be used to reconstituting the freeze-dried vaccine.
4. **Some of the commercial combination vaccines in the market:**

1	Indian Immunologicals Ltd	RAKSHATRIOVAC FMD+HS+BQ
2	Indian Immunologicals Ltd	RAKSHA BIOVAC HS+BQ
3	Intervet India Pvt Ltd	HS+BQ combined vaccine
4	Brilliant Industries Limited	HS+BQ vaccine
5	Ventri Biologicals	IBH+ND Inactivated vaccine
6	Brilliant Industries Limited	IBD+ND+IB Inactivated vaccine
7	Brilliant Industries Limited	IBD+ND+IB+EDS vaccine
8	Ventri Biologicals	LASOTA+IBD (live) vaccine
9	Sarabhai Zydus Animal Health Limited	ND+IBD+IB vaccine
10	Ventri Biologicals	ND+IBH killed vaccine

Conclusions

Combination vaccines are critical for continued success of vaccination programs. It is in the interest of developing countries to have combined vaccines in veterinary medicine, because they reduce production costs, increase convenience and efficacy concerning the logistics, thus lowering the cost of prophylactic projects. Although several potential combinations are being considered, the major drawbacks are basically due to the biological incompatibility of immunogens or immunosuppression and to the interaction of the various components when mixed, or when lyophilization is carried out. Hence, each new combination must be carefully & thoroughly studied in suitable animal models to ensure comparable safety and immunogenicity of the individual components.