# Animal Biologics: Past, Present and Future

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The common goal of producers, practitioners, and researchers is overall disease prevention and health improvement. This goal is accomplished by a combination of increased knowledge into disease mechanisms, better management systems, better disease monitoring systems and more effective prophylactic products and treatment methods.

This presentation will focus on the topic of animal biologics, which includes both preventative and treatment methods. We will discuss some aspects of the history of biologics, advances manifested in presently available products and futurisitc products and methods designed for cattle.

## Past

The concepts of resistance to infection were known centuries before the discovery of the germ theory of infectious disease. Thus elements of immunology preceded bacteriology, and long preceded virology. These fields have in turn been enhanced by the application of immunologic phenomena. Some of the major milestones in the development of immunology, specifically biologics, are presented below.

Preceding modern medicine, Chinese physicians in the eleventh century observed that the snorting of "snuff" made from the crusts of smallpox lesions prevented occurrence of the disease. Later in the Middle East the techniques of variolation, the intradermal application of powdered scabs, were used to "preserve the beauty of their daughters." This procedure reached England in the eighteenth century but was not fully accepted due to the widespread acceptance of "herb" medicine.

Around this time in western Africa a procedure was practiced by a nomadic tribe whereby material from lungs of contagious bovine pleuropneumonia *(Mycoplasma mycoides)* diseased cattle were inserted into cuts made in the skin over the nasal bones of unaffected cattle. This method was extremely effective although perforations into the nasal cavity often resulted. In 1770 a Dutch farmer, Reinder, discovered that he could inoculate materials from Rinderpest cases into young calves from dams of animals which recovered.

The person who is given credit for establishing vaccination as an accepted procedure was Edward Jenner in 1796. Jenner as a medical student made a surprising astute observation concerning milkmaids. This finding led to the inoculation of cowpox crusts into his "volunteer" assistant James Phillips and led to further studies that detailed the use of vaccination for disease prophylaxis. Following Jenner's success with cowpox for preventing human smallpox, attempts were made by veterinarians to use cowpox vaccinations to prevent a number of animal diseases. One veterinarian was heard to remark "if Jenner's procedure works for humans, why shouldn't it work for other animals?" Some of the same logic is used today.

The enhancement and further development of preventive immunization was made possible by Louis Pasteur who coined the term "vaccine" (from "vaccu," Latin for cow) in honor of Jenner's contribution. Pasteur's discoveries led to the development of the germ theory of disease when he established techniques for the *in vitro* culturing of microorganisms. During these investigations Pasteur observed that cultures of chicken cholera *(Pasteurella multocida),* when inadvertently left on the lab bench for the summer by an assistant, and then inoculated into fowl, produced no disease. Surprisingly, these fowl were resistant to subsequent infection with highly virulent organisms. Pasteur described this experiment as a "fowl foul-up." Many of Pasteur's concepts on the use of "modified-live" vaccine for viral and bacterial diseases are practiced today.

In 1896, Von Behring inoculated exotoxin from diphtheria bacillus into animals, who produced in their serum a toxin neutralizing substance called "antitoxin." The neutralizing capability could be transformed by serum into uninoculated animals, a process called "passive immunization." This work forms a model for the modern techniques of prophylaxis and/or treatment of disease through passive immunization. Thus, within a span of 15 years a series of fundamental discoveries about immunity were made and given practical application as therapeutic measures.

In the late 1890's, Loffler and Frosch observed that a filterable microorganism from cattle was associated with foot-and-mouth disease. This finding, along with others, led to the discovery of viruses. The word "virus" is Latin and is defined as poison or slime. Individuals who study viruses are often referred to in the same context, at least by many of their colleagues. It was not until the 1930's that it was observed that some viruses could be

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propagated in chicken embryos. The diseases encountered during World War II then led to the discovery of cell-culture propagation of viruses. This technological advance provided an opportunity for the isolation, identification and propagation of viruses. Additionally, the ability to *in vitro* culture viruses along with bacteria has led to large-scale propagation of these agents for immunization.

Thus prophylaxis for disease by vaccination became a basic principle and has been applied to most infectious agents identified to date.

## Present

In discussing biologics commercially available for cattle, one needs to include both vaccines and passage antibody treatment. Biologics for immunomodulation are being extensively evaluated for cattle and may be available in the not so distant future.

The goal of any vaccination procedure is disease prevention. Vaccines can be separated into categories based on their effectiveness and availability. Insofar as vaccines are concerned, one category consists of practical vaccines that work under field situations (e.g. MLV-Infectious Bovine Rhinotracheitis, *E. coli*). Experimental vaccines constitute the second category. In this instance the number of practical vaccines increases as vaccination procedures progress from experimental to commercial production (e.g. BVD subunit, BRSV subunit, pasteurella). The third type of category is one in which the vaccine is an unlikely prospect for success (salmonella).

Vaccines presently exist for most of the major infectious diseases of cattle. Some of the viral vaccines currently available in the U.S. include modified-live viral (e.g. IBR, BVD, BRSV) vaccines, killed viral vaccine (e.g. BVD, $PI_3$, IBR). Some of the bacterial vaccines available include killed bacterins (*E. coli,* Leptospira, Clostridia, and *P. haemolytica*), subunit (*E. coli* pili antigen). We have been overwhelmed in the last 5 years with the prospect of "genetically engineered" vaccines, especially subunit antigen produced from bacteria or other system. There are a number of genetically engineered products very close to being marketed.

Making the statement that vaccines are available for cattle diseases is gross oversimplification. There are numerous products available for all the major disease pathogens of cattle. In fact there are very few products that have made it to market that have employed such methodology. The biologics industry is extremely competitive. With the emergence of a number of genetic engineering firms working on animal products and in some cases the demise of some of these same firms, the number of biologies will increase. How does one decide which vaccine to utilize in practice? Unfortunately comparative efficacy studies on different products are usually not available. Thus, one often needs to personally evaluate products in the field.

*Evaluation of Vaccines in the Field*

A common fallacy among vaccine users is that efficacy can be accurately determined through extensive field usage of a vaccine in the absence of control animals. It should be noted that Eastern civilizations have used this approach for centuries. This belief may be well-founded for those diseases that are single-agent entities and are easy to diagnose. With more complicated disease problems, such as respiratory and enteric disease complexes, accurate field evaluation of a vaccine is extremely difficult. Without an adequate number of treatment and control animals, results often lead to erroneous conclusions. For example, a decrease in losses to neonatal calf diarrhea following vaccination of all animals in a herd may or may not be related to vaccine usage. Another example would be vaccination of breeding females in the midst of an abortion storm with IBR/BVD. You may observe a decrease in abortions but this finding could be due to natural spread of infection rather than vaccine protection. The sporadic nature of some diseases in the field and our lack of understanding why some animals become infected and some animals are refractory to infection necessitates that properly designed vaccine evaluation be conducted. Long market life of some vaccines, previously shown to lack efficacy, is evidence that our system of vaccine regulation is not fool-proof. This may reflect our inability to fully evaluate vaccine efficacy in the field.

Today's practitioner is faced with a multitude of animal biologies all produced for improving animal health. It is similar to trying to decide what breakfast cereal to buy when there are 500 brands in the store! If more comprehensive information were available on the various biologics, a decision to use one particular product could be based on vaccine efficacy rather than salesman efficiency.

## Future

Advances made in molecular biology, immunology and disease pathogenesis have brought changes in how we think about disease prophylaxis and treatment. We are starting to see vaccines that contain genetically engineered components. While genetically engineered vaccine components may be more efficacious in some instances, they will not be the panacea for all biologics, as some individuals announce. Other advances e.g. immunomodulation, may have as great an impact as genetically engineered vaccines.

The use of pseudorabies virus vaccines in swine is an example where genetic engineering has indeed influenced futuristic vaccine production. Both modified-live and subunit vaccines have been prepared via recombinant DNA techniques. Some of these products have recently gained

approval, others are undergoing clinical testing. The use of both PRV-MLV and subunit vaccines will allow for the differentiation of naturally exposed and vaccinated animals. Additionally these products are safer and hopefully more efficacious than current products.

The next generation of biological engineering will be manifested in the form of immunologic engineering. We will be able to modulate the different components of the immune system via the administration of various compounds. These compounds are selectively known as immunomodulators. Some immunomodulators are being evaluated in humans for cancer treatment. Interferon is an immune modulator which has the potential to provide nonspecific immunity to respiratory pathogens. In the near future swine herd health will include the administration of immunomodulators to swine of various ages to provide nonspecific immune stimulation (e.g. neonates, weaned pigs).

Another advance which will have an impact on disease treatment is the use of monoclonal antibodies. Monoclonal antibodies to *E. coli* pili antigens (K99) have been shown to be effective in treating newborn calves with severe colibacillosis. A problem with this product is the short half-life of the mouse-mouse monoclonal when administered to calves. Recently, bovine-bovine monoclonal antibody system has been reported. If this system is able to function on a large scale, we will see a re-emergence of passive antibody treatment for various diseases. These reagents will be less expensive than mouse monoclonal antibodies (e.g. Genecol 99) and will have a longer half-life because they will be produced in the host animal. The future in biologics will not be limited only to vaccines but for disease prophylaxis, will be expanded to include immunomodulators, passive antibodies for treatment, diagnostic kits for field disease evaluation and specific and nonspecific biological treatments (e.g. hormonal therapy to improve meat quality, influence fertility rate and influencing various other production parameters).



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