

In: **A Concise Review of Veterinary Virology**, Carter G.R., Wise D.J. and Flores E.F. (Eds.).  
International Veterinary Information Service, Ithaca NY ([www.ivis.org](http://www.ivis.org)), Last updated: 1-Mar-2006;  
A3406.0306

## Prevention of Viral Diseases, Vaccines and Antiviral Drugs

**D.J. Wise<sup>1</sup>, G.R. Carter<sup>2</sup> and E. F. Flores<sup>3</sup>**

<sup>1</sup>Department of Biology, Concord University, Athens, West Virginia, USA. <sup>2</sup>Virginia-Maryland Regional College of Veterinary Medicine, Virginia Tech, Blacksburg, Virginia, USA. <sup>3</sup>Department of Veterinary Preventive Medicine, Federal University of Santa Maria, Santa Maria, RS Brazil.

### Table of Contents

**General**  
**Vaccines**  
**Passive Immunization**  
**Herd Immunity**  
**Antiviral Drugs**  
**Glossary**

### **General Preventing Infection**

The only certain way to prevent viral infection is to prevent exposure. This is accomplished in practice by only allowing those animals without evidence of previous exposure to commingle. This restricted contact is often referred to as "closed herds". To effectively maintain this closed status, all replacement animals and show animals must be isolated from the remaining animals for at least 2 - 3 weeks.

During this time, they are monitored for clinical signs and tested serologically (or virologically) for evidence of exposure. Preventing exposure through restricted contact is quite effective in areas where particular viruses are relatively uncommon, but is impractical in areas where these viruses are endemic. In such instances, efforts are redirected from preventing "infection" to preventing disease.

### **Controlling Infection and Disease**

Fundamental to controlling viral infections and disease are good management practices. Stress factors play important roles in predisposing animals to infection and in the spread of disease. Particularly important are the stresses associated with poor nutrition, overcrowding, and housing with improper ventilation.

Management practices should include preventative measures to protect the fetus and the newborn. Some viruses that cause mild or unapparent infections in adult animals may cause abortions or serious disease in neonates (e.g. parvovirus in swine). Thus, efforts should be made to restrict the contact of pregnant animals and newborns from other animals. It is also important to insure that the newborn receives colostrum, which contains antibodies that would confer protection during the first weeks of life.

Another aspect of good management is the need to minimize contact between different species of animals, as some viruses cause unapparent infections in one species but severe disease in others. An example is the pseudorabies virus, which causes subclinical infections in older pigs but is frequently fatal in piglets, sheep, dogs and cats.

Thorough cleaning and disinfection, the use of clean coveralls and footbaths, are essential to prevent the spread of viruses by fomites (see Table 6.1). These aspects of management should be practiced at all times, but especially during disease outbreaks. When a disease outbreak occurs, all animals should be quarantined (isolated and observed) and, if indicated, treated symptomatically. For instance:

- Receive the necessary supportive therapy, as fluid replacement in severe cases of diarrhea.
- Aqueous sodium chlorite solution is effective for disinfection. See Table 6.1 for other disinfectant choices.
- Treatment with antibiotics may be advisable to prevent secondary bacterial infection.

Table 6.1. Some Common Commercially Available Antiviral Disinfectants*			
Disinfectant	Examples	Uses	Comments
Alcohol	Ethyl, isopropyl	Hands, thermometers	Moderately virucidal at 70 - 80 %; ethanol is preferable
Chlorhexidine	Hibitane, Nolvasan	Many uses including examination tables, cages, other surfaces	Tolerant to the presence of organic compounds, body fluids, etc.; expensive
Detergent iodophores	Betadine, Wescadine, Redene	Drinking water, food and utensils, dairies, spot disinfection	Action based release of iodine & detergent action; less affected by high protein; expensive
Ethylene dioxide		For heat sensitive materials	Available as a compressed gas at 10% with 90% CO <sub>2</sub> , otherwise toxic and explosive
Formaldehyde	Formalin	Laundry & bedding surfaces; as a vapor for other surfaces	Low power of penetration; irritating hypersensitivity occurs
Glutaraldehyde	Cidex	Cold sterilization of instruments with lenses	2% solution buffered with sodium bicarbonate; virucidal (10 min., pH 7.5 - 8.5); expensive
Phenol derivatives	Lysol, Dettol, Staphene, Sudol	Hands, examination tables, cages, other surfaces	2.5% aqueous solution; efficacy dependent on concentration and temperature; high protein decreases effectiveness
Quaternary ammonium compounds	Zephiran, Roccal, Savlon	Zephiran (benzalkonium chloride) used for cleaning wounds	Not effective against many viruses; high protein decreases effectiveness
Sodium hypochlorite	Chlorox, Chlorize	Same as detergent iodophores	Highly effective, rapid action; high protein decreases effectiveness; irritating; inexpensive
*This information applies to most viruses; there are some exceptions.			

## Vaccines

In some instances, disease prevention can be accomplished through vaccination. While vaccination doesn't necessarily prevent infection, the previous "priming" of the host's immune system allows for a quick response and clearance of the virus before disease occurs or mild disease of shorter duration. Indeed, vaccination is the most effective and cost-benefit among all preventive measures in animal health.

There are two principal types of vaccines that are widely used in veterinary practice, those made with killed virus (inactivated) and those prepared with modified-live (attenuated) virus.

Killed virus vaccines consist of viruses, generally cultivated in tissue culture or embryonated eggs that have been chemically inactivated, often with formalin or beta-propiolactone. These vaccines frequently contain adjuvants to make them more immunogenic. Killed virus vaccines generally require more than one dose to induce immunity and periodic booster doses to maintain adequate immunity. Inactivated vaccines often induce an immunity that is less protective and of shorter duration than that induced by modified live vaccines. Advantages of killed vaccines: they do not revert to virulence and they are safe for use in pregnant and immunocompromised animals.

Modified-live virus vaccines consist of viruses that have been made less virulent by some means. This is usually accomplished by the serial cultivation of the virus in cell cultures, embryonated eggs, or laboratory animals. Viruses can also be attenuated by deleting specific genes responsible for virulence. This genetic manipulation was used to make a commercially available pseudorabies vaccine. Attenuated vaccines generally confer lifelong immunity, since the vaccine virus replication mimics the natural infection. A sufficiently attenuated live vaccine should not cause disease in healthy vaccinated animals; however, it may cause disease in immunocompromised individuals and fetuses. Some modified-live virus vaccines can be administered by the oral, nasal, or genital (preputial, vaginal) routes where they elicit a local

secretory antibody response (IgA).

The main disadvantage to modified-live vaccines is that some may cause mild disease, lethal infections of the fetus, and the possibility that the attenuated virus may regain its virulence. Live vaccine virus may be transmitted to contact animals.

Several new approaches are being explored in an effort to make vaccines safer and more effective. Some of these approaches are briefly as follows:

**A subunit vaccine** is a type of inactivated vaccine that contains the portions (proteins, fragments) of the virus necessary to induce immunity.

**Synthetic peptides** are produced by chemical synthesis of smaller portions (peptides) of viral proteins and employed as more refined subunit vaccines.

**Recombinant vaccines** are of three kinds as follows:

**Recombinant proteins:** The gene for the target viral antigen is cloned and the cDNA introduced to a bacterium or yeast via a plasmid either of which produces large amounts of antigen. This antigen is then used as a vaccine.

**Viral vectors:** The gene (or genes) from a large virus (usually poxvirus, herpesvirus or adenovirus) is deleted and replaced with a gene (or genes) that encodes the desired antigen (or antigens); the latter are introduced to the animal and expressed in infected cells. The virus that carries the genes of the desired antigen is called a vector.

**Gene-deleted vaccines:** The virulent virus is made less virulent by gene deletion or by replacing key regions of genes with other genetic material. Several recombinant vaccines are being used, including the human hepatitis B virus protein expressed in yeast; rabies virus protein expressed in vaccinia virus; F and G proteins of canine distemper virus inserted into the genome of canarypox virus.

**Anti-idiotypic vaccines:** Anti-idiotypic antibodies are made in a two-step process. First an antigen is introduced, to which an organism has an immune response. These antibodies are then used to immunize a second individual, to which an immune response is made. Some of these antibodies have the antigenic characteristics of the original antigen. These are called anti-idiotypic antibodies. Thus far anti-idiotypic vaccines have only been used experimentally.

**DNA vaccines:** In this approach, the viral gene(s) of the protein antigen is introduced to the subject via a plasmid, stimulating the production of a specific, protective viral antibody. Thus far this type of vaccine primarily has been used experimentally. In an effort to find an effective vaccine to prevent a potential influenza pandemic the DNA vaccine approach is being investigated. Their efficacy in humans to generate an appropriate immune response has yet to be established. However, a DNA vaccine has been licensed in the USA for the prevention of West Nile virus infection of horses.

**Marker vaccines:** These unique vaccines either lack a characteristic peptide or possess a novel peptide that is not present in the wild type strains of the virus. Thus the missing peptide or novel peptide can serve as a marker for the vaccine strain of a particular virus. They enable diagnostic tests to differentiate between vaccinated and carrier or infected animals. The diagnostic serological test detects antibody to the wild type virus but not to the vaccine altered virus. The methods used to create marker vaccines are gene-deletion (lack of a peptide) or creation of a subunit vaccine (novel peptide). Marker vaccines are commercially available and include pseudorabies (deletion vaccine) and bovine herpes virus -1 (deletion vaccine), vaccines and others are currently being developed for other diseases.

### ***In Ovo Vaccination***

This form of vaccination is practiced for the prevention of Marek's disease.

Embryonated eggs are inoculated with an automatic device at 18 days of incubation. The procedure, which is safe and effective, is also used to vaccinate against infectious bronchitis and infectious bursal disease.

In general, effective vaccines are available for those viruses that have one or a few stable antigenic types and that can be obtained in sufficient quantity for vaccine preparation. Interestingly, it is because of antigenic instability that the composition of the human influenza vaccine has to be regularly (annually) changed, in accordance with the current strains circulating among the population.

### **Passive Immunization**

Passive immunization refers to the transfer of immunoglobulins to non-immune individuals. The immunoglobulins present in immune sera contain neutralizing antibodies that prevent the attachment of the specific virus to susceptible cells. Natural passive immunity includes the receipt of maternal antibodies via placenta (IgG), colostrum (IgG) or the amniote egg yolk (IgY). Receipt of inadequate levels of maternal antibody can result in high morbidity and mortality rates for many viral diseases of young animals.

In clinical practice, immunoglobulins are generally given before exposure or during the incubation period to modify the infection. Antiserum (produced in donor animals) protects for a short period of time and has very limited use in the prevention of viral diseases. Antisera have been used to prevent canine distemper, feline panleukopenia and West Nile virus infection in horses. In some horse and cattle herds, storage of colostrum with subsequent administration to neonates is used to increase their immunity.

## Herd Immunity

This phenomenon occurs when a sufficiently large proportion of a population ("herd") has been immunized and thus is immune to a particular virus. An individual that may eventually lack immunity to the same virus is then protected, as the remainder of the herd is incapable of transmitting the virus. In order to be effective, the vaccine in question must prevent the disease caused by the virus and its transmission. A similar effect can be seen with natural disease, if the majority of a population had recovered from a disease and possesses long-term immunity, then a few non-infected individuals could be protected by herd immunity as long as there were no reservoir animals in the herd.

## Antiviral Drugs

Antiviral drugs have had very limited veterinary use. It seems likely that some of these drugs will be effective against animal viruses that are closely related to the human viruses against which they have shown efficacy.

These drugs can be separated into two large categories based upon mode of action. These are the nucleoside analogs and non-nucleoside analogs discussed below.

In 2006, the CDC reported that a human type A flu strain had developed resistance to two commonly used antiviral drugs, rimantadine and amantadine. The flu strain H3N2, predominant in the flu season, once routinely treated with these antiviral drugs has developed resistance. This information supports the need for the development of additional antiviral drugs and potentially the use of antiviral drug cocktails for treatment of influenza.

## Nucleoside Inhibitors

Many of the commercially available antiviral drugs are nucleoside analogs, which affect viral nucleic acid polymerases. The more common of these are: acycloguanosine (acyclovir), dihydroxypropoxy-methylquanine (ganciclovir), adenine~arabinoside (vidarabine), and azidothymidine (zidovudine). See Table 6.2 for a list of some of the nucleoside inhibitors and typical viruses they are used to treat.

<b>Nucleoside Inhibitor</b>	<b>Type of Analog</b>	<b>Viruses Targeted</b>
Acyclovir	Guanosine analog	Herpes simplex virus Varicella-zoster virus
Ganciclovir	Guanosine analog	Cytomegalovirus
Cidofovir	Cytosine analog	Cytomegalovirus Human papillomavirus
Vidarabine	Adenine with arabinose sugar	Herpes viruses
Iododeoxyuridine	Thymine analog; iodine in place of methyl group	Herpes simplex virus
Trifluorothymidine	Thymine analog; 3 fluorine atoms in place of 3 hydrogen atoms	Herpes simplex virus
Azidothymidine	Thymine analog; azide group in place of hydroxyl group of ribose	Human Immunodeficiency virus
Dideoxyinosine	Inosine lacking the 3'-OH group	Human Immunodeficiency virus
Dideoxycytidine	Cytosine lacking the 3'-OH group	Human Immunodeficiency virus
Stavudine	Thymine analog	Human Immunodeficiency virus
Lamivudine	Cytosine analog	Human Immunodeficiency virus Hepatitis B virus

Table 6.2. Properties of Various Nucleoside Inhibitors		
Nucleoside Inhibitor	Type of Analog	Viruses Targeted
Abacavir	Guanosine analog	Human Immunodeficiency virus
Tenofovir	Adenosine monophosphate analog	Human Immunodeficiency virus
Ribavirin	Guanine precursor analog	Respiratory syncytial virus Influenza B virus

Antiviral drugs are not widely used, in veterinary medicine. Acyclovir is effective against herpesviruses and has been used to treat ocular herpesvirus infection of cats. This drug has also been used to prophylactically treat expensive psittacine birds that have been exposed to psittacine herpesvirus.

### Non-Nucleoside Inhibitors

Interferons and antiviral drugs are used for the specific treatment of viral diseases. Interferons were previously discussed in detail in chapter 5. They are of importance in antiviral therapy as interferons appear early in infection and play a major role in recovery. The mode of action is the inhibition of viral protein synthesis.

The treatment of animals with exogenous interferon is not practiced widely because of the general unavailability of host-species interferons. While interferons are not necessarily host-species specific, their action is dependent upon their ability to bind to specific cell surface receptors. Human  $\alpha$ -interferon, which is commercially available as a DNA recombinant, has some cross-species activity and has been used to orally treat cats infected with feline leukemia virus.

- In addition to interferons, other drugs that inhibit viral mRNA translation are fomiversin and methisazone. Fomiversin (Vitravene) is an antisense DNA that blocks replication of cytomegalovirus. Methisazone (N-methylisatin- $\beta$ -thiosemicarbazone) is specific for poxvirus mRNA.
- Amantadine (Symmetrel) and rimantadine (Flumadine) interfere with the penetration and/or uncoating of many enveloped viruses, but is effective only against influenza A infections in humans. These antivirals are not commonly used in the U.S.
- Saquinavir (Invirase), indinavir (Crixivan), ritonavir (Norvir), and nelfinavir (Viracept) are inhibitors of viral proteases. They act by binding the active site of the protease, inhibiting the enzyme from cleaving other proteins. These drugs are often used in drug cocktails for the treatment of HIV infection in humans.
- Zanamivir (Relenza) and oseltamivir (Tamiflu) inhibit the release of virus from the host cell. They are specific for the neuraminidase of influenza virus, prevent release, and thereby limit spread of the virus.

### Glossary

**Adjuvants:** Substances or chemical formulations used to enhance the immune response to inactivated vaccines. They act by retaining the immunogen at the injection site, as by a depot effect, and thus delaying its release; the antigenic stimulation is prolonged and consequently increased. Some adjuvants may also stimulate macrophages, lymphocytes and other cells involved in the immune response. Salts of metals, such as those of aluminum, oil emulsions (Freund's adjuvants), and synthetic lipid vesicles (liposomes) are some of the adjuvants used.

**Neuraminidase:** A glycoprotein which is present as a spike on the outside of the influenza virus envelope. It breaks down an inhibitor of the influenza virus hemagglutinin protein.

All rights reserved. This document is available on-line at [www.ivis.org](http://www.ivis.org). Document No. A3406.0306

