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Forty Years of Canine Vaccination

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I. Introduction

With the exception of rabies vaccines, which were introduced earlier this century, efficacious canine vaccines for the protection from infectious diseases were developed during the past 40 years. Research and development during this time period has focused on controlling fatal infectious diseases like canine distemper, infectious canine hepatitis, canine parvovirus infections, or leptospirosis. Later developments addressed the need to control nonfatal diseases such as kennel cough or Lyme disease.

Modified live virus (MLV) vaccines became the products of choice to control fatal virus infections in dogs. They induce rapid and prolonged cellular as well as humoral immune responses after a single inocula-

tion in susceptible animals. Historically, inactivated (killed) virus vaccines did not sufficiently control disease induced by canine distemper virus (CDV) or canine parvovirus (CPV).

Inactivated virus vaccines were successfully developed to prevent rabies virus infections. Inactivated bacterial products (bacterins) protected dogs from certain strains of leptospirosis, *Bordetella bronchiseptica*, and *Borrelia burgdorferi* (Lyme disease).

The induction of mucosal immunity by intranasal inoculation of modified live products provided better protection against infectious agents that cause kennel cough than parenteral inoculation with inactivated products.

A recombinant vaccine for canine distemper that was introduced recently may be the beginning of a new era in vaccine production. It was intended to increase the safety level of vaccination. However, the efficacy of this vaccine is probably not comparable to MLV vaccines. More recombinant vaccines can be expected to appear on the market. Undoubtedly, DNA vaccines will be introduced for some of the canine infectious diseases which may have a similar effect. In most cases in vaccine production, the enhancement of one factor comes at the sacrifice of the other. There is presently a tendency to produce safer products. The question remains whether the safer products sufficiently control disease outbreaks.

It appears that canine infectious diseases are presently controlled well by vaccination. This may be the time for some fine tuning to address lesser problems such as the possible autoimmune responses in some breeds after multiple vaccinations. The question has been raised: "Are we vaccinating too much?" and the answer is probably yes. Limited data are available for the duration of a vaccine-induced immunity against CDV, CPV, and canine adenovirus (CAV) in dogs kept in isolation. Immunity against these diseases lasts for several years and annual revaccinations may be unwarranted. In addition, if reliable and affordable quick tests for levels of maternal antibody were to become available, the multiple puppy vaccinations could be reduced to one or two inoculations. The use of oro/nasal vaccinations could be developed for more products, perhaps combined with newly developed vectors, which may reduce the risk of abnormal reactions after needle inoculations. There will be additional innovations to reduce the risk of vaccination but to maintain the protection of the animals.

The purpose of this paper is to give a brief, historical review of canine vaccine development during the past 40 years.

II. Rabies Virus

Rabies in dogs has been known since the fifth century B.C. and the dog has long been known to be a principal transmitter of rabies.

The first rabies vaccine was developed by Pasteur in the early 1880s when he adapted "street" virus to rabbits by serial intracerebral passage (Pasteur, 1885). The Pasteur vaccine was predominantly used for human vaccination. Chloroform or ether inactivated virus vaccines for dogs prepared from infected brain suspensions became available in the 1920s (Kelsner, 1930). The development of live attenuated rabies virus, vaccines in low egg passage (LEP) and high egg passage (HEP) (Koprowski, 1954) led to effective vaccination of dogs (Tierkel *et al.*, 1953; Sikes, 1975). However, on rare occasions the live attenuated vaccines caused rabies-like disease in dogs. They are no longer available. Greatly improved inactivated virus vaccines prepared from rabies virus grown in diploid cell culture are now commonly used in dogs (Pastoret *et al.*, 1997). Although antigenic differences between virus strains were found by monoclonal antibody, the vaccines cross-protect against different strains (Wiktor and Koprowski, 1980). Most of the inactivated rabies virus vaccines on the market today induce immunity in dogs that lasts for 3 years.

Promising results have been reported with rabies ISCOMES (Osterhaus *et al.*, 1986). In addition, newer developments include viral vectors expressing rabies virus G protein. The vectors are nonreplicating in mammalian hosts (avipox viruses). Both fowlpox and canarypox recombinant rabies vaccines induced protective immunity in dogs and proved to be safe (Taylor *et al.*, 1988, 1991).

In several countries around the world, canine rabies was greatly reduced by mass immunization of dogs (Bögel *et al.*, 1982). A great reduction in wildlife rabies, the source for dog rabies, has been accomplished by the introduction of live attenuated rabies virus by the oral route (Baer *et al.*, 1971). Initially a MLV vaccine was applied that was later replaced by a vaccinia recombinant rabies vaccine (Pastoret *et al.*, 1997). Results with oral vaccination of dogs remain inconclusive.

III. Canine Distemper Virus

Canine distemper (CD) is caused by a morbillivirus closely related to measles and rinderpest viruses. The first vaccine against CD was made by Puntoni (1923) from formalin inactivated brain tissue from

dogs with distemper encephalitis. Inactivated CDV vaccines, which were used earlier this century, have not been able to control the disease and are no longer commercially available in the United States. They include a limited protection against disease and no protection against infection. Another approach was attempted by Laidlaw and Dunkin in the late 1920s (1928) by simultaneous inoculation of virulent virus and antiserum. Results were not satisfactory. Vaccination with the heterotypic measles virus (MV) induces protection from disease but not from infection with CDV (Appel *et al.*, 1984). It has the advantage of inducing partial immunity in pups with maternal antibody (reviewed by Appel and Gillespie, 1972).

The first MLV vaccine for CD was developed by Green and Carlson (1945) by passaging virus 50 times in ferrets. The vaccine was widely used. Unfortunately, clinical signs and death frequently occurred after vaccination.

The MLV vaccines for CD that have controlled the disease and that are still in use today were developed in the late 1950s. The virus was adapted to embryonating hen eggs by Cabasso and Cox (1952, Lederle strain) and by Haig (1956, Onderstepoort strain). Both strains were later adapted to tissue culture. Rockborn (1960) introduced a canine kidney cell culture adapted CDV vaccine that is still used worldwide today. There are advantages and disadvantages in both types of vaccines. The Rockborn vaccine induces complete immunity in virtually 100% of susceptible dogs. However, products from some companies induce postvaccinal encephalitis (PVE), which has not been seen in 35 years of the original and authentic product from Behringwerke (Hoechst) in Germany. The Onderstepoort strain does not induce PVE, however, the seroconversion rate of this product in general is lower, and its H glycoprotein profile differs from the H protein of field isolates (Harder *et al.*, 1996).

A promising approach was taken by De Vries *et al.* (1988). They incorporated the CDV-H and -F proteins into immune stimulating complexes (ISCOMES), which protected dogs from CDV infection. Because both the H and the F proteins are important in producing immunity against CDV, any future recombinant or DNA vaccine should incorporate both. In 1997, a recombinant CDV vaccine containing the H and F genes in a canarypox virus carrier was introduced (Stephensen *et al.*, 1997).

IV. Canine Parvovirus

A new enteric disease of dogs that resembled panleukopenia of cats and mink enteritis appeared in 1978 in North America, Europe, and

Australia. A parvovirus was isolated (Appel *et al.*, 1979) and was tentatively classified as canine parvovirus type 2 (CPV-2) (Carmichael and Binn, 1981). This was in contrast to the "minute virus of canines" that was isolated in 1967 and was referred to as canine parvovirus type 1 (Binn *et al.*, 1970). CPV-2 is believed to be a mutant of feline panleukopenia virus (FPV) or mink enteritis virus; however, the origin of this "new" virus remains unknown.

Soon after the detection of CPV-2 inactivated and heterotypic (FPV) vaccines were introduced that controlled the disease only to a limited extent (Appel *et al.*, 1979; Pollock and Carmichael, 1982). A ML-CPV-2 vaccine became available in 1980 (Carmichael *et al.*, 1981, 1983; Pollock and Carmichael, 1983) that was safe and more efficacious than the inactivated or heterotypic vaccine. The vaccine protects dogs from infection as well as from disease. Antibody titers of $\geq 1:80$ tested by H1 are considered to be protective. Dogs vaccinated with ML-CPV-2 vaccine and kept in isolation thereafter had protective antibody titers at least 5 years after vaccination (L. E. Carmichael, personal communication).

CPV-2 has further mutated into CPV-2a and CPV-2b and new vaccines have been introduced (Parrish, 1991). However, the original ML-CPV-2 vaccine protects dogs against present field strains of CPV-2 (Appel and Carmichael, 1987).

Vaccination failures are frequently found when maternal antibody interferes with immunization. Pups become susceptible to virulent CPV-2 before they are susceptible to vaccination. This "window" of susceptibility may last from 2 to 5 weeks (Pollock, 1984). Although claimed by vaccine producers, none of the presently available vaccines eliminates this "window" entirely.

V. Canine Coronavirus

Canine coronavirus (CCV) causes a mild gastroenteritis in dogs (Appel *et al.*, 1980; Carmichael and Binn, 1981). However, it may enhance the pathogenicity of CPV-2 infection (Appel, 1988). The virus was first isolated from sentry dogs with diarrhea in 1971 (Binn *et al.*, 1975). The distribution of the virus in dogs appears to be worldwide (Pensaert and Callebaut, 1978; Rimmelzwaan, 1990).

Inactivated CCV vaccines were introduced in the 1980s (Edwards *et al.*, 1985). The vaccine protects dogs from disease but not from infection. Because of the mild nature of the disease and the limited protection by the killed vaccine its use in dogs is debatable.

In 1983 a ML-CCV vaccine was introduced in combination with other canine vaccines including CPV and CDV. The vaccine was withdrawn from the market 2 months later because adverse reactions were seen in more than 900 dogs with central nervous signs or death in more than 300 dogs (Martin 1985; Wilson *et al.*, 1986).

A different strain of ML-CCV was recently licensed in the United States, which by itself appears to be safe and efficacious. However, in combination with ML-CDV (Rockborn strain), it produced PVE in a large number of dogs. The combination was withdrawn from the market and replaced with the same ML-CCV, but a canarypox vectored CDV that is incapable of causing PVE. A ML feline enteric coronavirus vaccine antigenically related to CCV also became available recently.

VI. Canine Adenovirus Type 1 (Infectious Canine Hepatitis Virus)

Infectious canine hepatitis (ICH) or hepatitis contagious canis (HCC), formerly known as "epizootic fox encephalitis," is caused by canine adenovirus type 1 (CAV-1). A comprehensive report about the disease in dogs was made by Rubarth in 1947. Besides acute hepatitis, CAV-1 is known to be responsible for other diseases (e.g., encephalopathy, neonatal disease, respiratory disease, chronic hepatitis, interstitial nephritis, and ocular lesions) (reviewed by Koptopoulos and Cornwell, 1981). The virus was isolated and production of a MLV vaccine followed after serial passage in dog or swine cells (Cabasso *et al.*, 1954, 1958). The safety of this product was limited; the vaccine induced "blue eyes" in some dogs, was shed in urine, and produced kidney lesions. The CAV-1 vaccine for the control of ICH was replaced in the 1970s by CAV-2 vaccines, which induce protection from ICH virus infection without the undesirable side effects of CAV-1 vaccines (Appel *et al.*, 1975).

Inactivated vaccines for CAV-1 are not on the market in the United States. (*Editor's note:* A vaccine now manufactured by Bayer Animal Health [previously BioCor, previously Tech America] still contains an inactivated CAV-1 component according to the package insert. It also contains inactivated CAV-2.) They are available in other countries and have been found to be safe and efficacious for limited time periods (Miller *et al.*, 1980).

VII. Canine Adenovirus Type 2

In 1961 a virus designated Toronto A26/61 was isolated by Ditchfield *et al.* (1962) from dogs in Canada suffering from laryngotracheitis and kennel cough. The virus is one of the agents causing severe kennel cough

in nonvaccinated puppies in pet shop situations that may simulate canine distemper (Appel, 1981). It was found to be antigenically related to CAV-1; however, the tissue tropism of both viruses is entirely different (Appel *et al.*, 1973). The virus was later classified as CAV-2 (Hamelin *et al.*, 1984; Marusyk *et al.*, 1970). The attenuated CAV-2 proved to protect dogs against infection with both CAV-1 and CAV-2 (Appel *et al.*, 1975). Because ML-CAV-2 vaccine is safer than CAV-1 vaccine, the former replaced the latter in the 1970s. Intranasal vaccine is now available in combination with *B. bronchiseptica* and canine parainfluenza virus to protect dogs from kennel cough. It has the advantage over parenteral injection by inducing immunity in pups with maternal antibody (Appel *et al.*, 1975) and, therefore, only one inoculation is needed.

VIII. Canine Parainfluenza Virus

Canine parainfluenza virus (CPIV) is one of the main causes of canine infectious tracheobronchitis or "kennel cough" and has a worldwide distribution (Appel and Percy, 1970; Binn and Lazar, 1970). The virus was first isolated from laboratory dogs with respiratory disease (Binn *et al.*, 1967). CPIV is closely related to simian virus 5 (SV5) (Binn *et al.*, 1967; Crandell *et al.*, 1968), and to human parainfluenza 2 (Hsiung, 1972).

Attenuated CPIV vaccines were introduced in the 1970s in combination with *B. bronchiseptica* in two forms: One with inactivated *B. bronchiseptica* for parenteral inoculation (Chladek *et al.*, 1981; Emery *et al.*, 1976) and one with ML *B. bronchiseptica* for intranasal inoculation (Glickman and Appel, 1981; Kontor *et al.*, 1981). Because protection from infection by both agents depends on mucosal immunity with IgA production, the latter protects from infection and disease while the former protects only from disease. In addition, maternal antibody does not interfere with the intranasal application. More recently a ML-CAV-2 component has been added to the intranasal vaccine. CAV-2 is also involved in the kennel cough complex. A genome analysis of virulent and attenuated strains of CPIV was made by Yonezawa (1985).

Although CPIV vaccine-induced immunity probably lasts longer than 1 year, annual revaccination with the combined vaccine is recommended because immunity to *B. bronchiseptica* is limited.

IX. *Bordetella bronchiseptica*

Bordetella bronchiseptica is the main cause of canine infectious tracheobronchitis or "kennel cough," a highly contagious respiratory dis-

ease of dogs (Bemis *et al.*, 1977a; Binn *et al.*, 1968; Wagener *et al.*, 1984; Wright *et al.*, 1973). Infection with *B. bronchiseptica* is not restricted to dogs. A variety of other species become infected with the agent including pigs, cats, and rodents. Although *B. bronchiseptica* is highly susceptible to antibiotics *in vitro*, the *in vivo* effect is limited because the organisms attach to the cilia of trachea and bronchi (Bemis and Appel, 1977; Bemis *et al.*, 1977b).

The immune response to *B. bronchiseptica* in dogs is slow. Although dogs become resistant to reinfection and clearance is initiated by 3 weeks after infection, total clearance of the bronchial tree takes about 3 months (Bemis *et al.*, 1977b). The mucosal immunity resulting from infection or intranasal vaccination lasts for about 1 year (Bemis *et al.*, 1977b). Mucosal immunity with IgA production is essential for protection from infection.

As with CPIV, two forms of vaccine have been developed: one inactivated bacterin in adjuvant for parenteral inoculation (Chladek *et al.*, 1981; McCandlish and Thompson, 1978) and one ML in combination with CPIV for intranasal installation (Bey *et al.*, 1981; Glickman and Appel, 1981; Kontor *et al.*, 1981; Shade and Goodnow, 1979). The latter protects from infection with virulent *B. bronchiseptica* and from disease while the former protects only from disease. Two inoculations of susceptible pups are needed to induce protection. Maternal antibody does not interfere with intranasal vaccination and only one inoculation is needed. In addition, parenteral inoculation with killed organisms and adjuvant may cause undesired local reactions.

X. *Borrelia burgdorferi*

Lyme disease or Lyme borreliosis is caused by the spirochete *Borrelia burgdorferi* (Barbour, 1984). The agent is transmitted by hard shell ticks (*Ixodes* species) (Spach *et al.*, 1993; Appel, 1990). Lyme disease is seen in humans (Steere, 1989), dogs (Appel *et al.*, 1993; Levy *et al.*, 1993), cats (May *et al.*, 1994), horses, and cattle (Parker and White, 1992) after natural infection. The disease in humans on the North American continent was first described by Steere *et al.* (1978) and in dogs by Lissman *et al.*, 1984).

For vaccination strategies it has to be taken into consideration that Lyme disease in the United States is caused by *B. burgdorferi sensu stricto*. Additional strains of *B. garinii*, *B. afzelii*, and *B. japonica* are known to occur worldwide. Cross-protection between strains is limited (Lovrich *et al.*, 1994). In addition, Lyme disease is prominent in endemic areas. Ninety percent of Lyme disease in the United States was

found in the Northeast, with the upper Mississippi region and Northern California following in frequency. Vaccination of dogs should only be recommended in endemic areas and in dogs exposed to ticks. It has been commented that only 5% of seropositive dogs develop clinical lameness that responds well to antibiotic treatment. However, a high percentage of exposed nonlame dogs have a subclinical chronic polyarthritis (Appel *et al.*, 1993) and antibiotic treatment does not entirely eliminate persistent infection (Straubinger *et al.*, 1997a,b). In addition, a fatal renal syndrome has been observed in a limited number of dogs (Dambach *et al.*, 1997).

A whole-cell bacterin for dogs was introduced in 1992 by Chu *et al.* A single protein vaccine for dogs prepared from recombinant outer surface protein A of *B. burgdorferi* became available in 1996 (Ma *et al.*, 1996; Chang *et al.*, 1995). The OspA vaccine has the advantage that it induces a specific borreliacidal antibody in dogs (or other species) that prevent transmission of *B. burgdorferi* from ticks to dogs (Straubinger *et al.*, 1995). OspA vaccines for human Lyme disease are in testing stages. (*Editor's note:* Extensive research attempting to demonstrate infection and disease from *B. burgdorferi* in cattle, calves, fetuses *in utero*, and adult pregnant cows by Schultz and others in 1993 showed that cattle are highly resistant to infection and no clinical disease was produced in any aged animal, including young fetuses, when multiple isolates of *B. burgdorferi* were given at low or high doses.)

XI. Leptospirosis

Leptospirosis is a zoonotic disease of worldwide distribution. The disease may be fatal in dogs if left untreated (Hartman *et al.*, 1986). Dogs may recover clinically after antibiotic treatment but may die from kidney failure and uremia several months or years later. The disease is caused by infection with antigenically distinct serovars of *Leptospira*. The most common serovars isolated from dogs used to be *L. icterohaemorrhagiae*, *L. canicola*, *L. pomona*, and *L. grippityphosa*. However, in recent years outbreaks of leptospirosis in dogs infected with different serovars have been reported from Canada and Long Island. Raccoons, opossums, deer, rodents, and domestic livestock are reservoirs for most *L. serovars* with the exception of *L. canicola*, which is transmitted from dog to dog.

Bivalent bacterins for dogs that contain *L. canicola* and *L. icterohaemorrhagiae* have been on the market since the 1950s (Hartman *et al.*, 1984a,b). They are prepared from chemically inactivated whole cells, which make them relatively allergenic. Because immunity after

vaccination is highly serovar specific, immunized dogs are not protected from other types that are common in many areas and that may infect dogs. They may also suppress the immune response in young puppies and vaccination of pups less than 9 or 10 weeks of age should not be recommended. In addition, the vaccine-induced immunity in dogs is often less than 6 months, and repeated vaccination in endemic areas would be essential for protection (Broughton and Scarnell, 1985). It would be highly desirable to have specific outer surface (envelope) proteins for the immunization of dogs (Bey and Johnson, 1982) like the OspA vaccine in Lyme disease, another spirochetal disease, to reduce the risk of anaphylactic shock and other vaccine-related disorders. In addition, more serovars should be included in leptospira vaccines that correlate with the serovars in endemic areas.

Public health considerations: *Leptospira*-contaminated urine is highly infectious for people. Persistent infection in healthy vaccinated dogs with leptospiuria has been found with resulting development of the disease in people (Feigin *et al.*, 1973).

XII. Summary

During the last 40 years vaccines have been developed that have greatly reduced the incidence of infectious diseases of dogs. In general, modified live products have been superior to inactivated vaccines for dogs. It can be expected that recombinant and/or DNA vaccines may dominate the market in the future.

Although most vaccines on the market are safe and efficacious, there have been exceptions where disease was induced by vaccination or dogs were not protected. The failure of protection may in part be due to variations in individual vaccine batches. Only potency tests but not efficacy tests are required, which may not be sufficient. For example, a virus titer in a vaccine may be meaningless if the minimum protective dose is not known. Overattenuated virus (e.g., CDV-Ond or parvovirus in cat cells) may have a high titer in tissue culture but is not immunogenic.

The question of frequency of vaccination of dogs should be addressed. Annual revaccinations for CDV, CPV, and CAV are probably not needed. However, it would be desirable to collect more data to support less frequent vaccinations. Annual immunization for bacterial diseases such as kennel cough, Lyme disease, and leptospirosis should continue. It also would be desirable to develop more oro/nasal vaccines, perhaps combined with newly developed vectors that are less likely to induce undesirable side effects that may be seen after parenteral vaccination.

Finally a word of warning against homeopathic "nosodes" to replace

tested canine vaccines. They will appear highly effective as long as the majority of dogs remain vaccinated. As soon as a nonvaccinated dog population is large enough to allow virulent agents to spread, disease outbreaks will occur and we will be back where we began 40 years ago.

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