DEVELOPMENT OF AN ORAL DOG RABIES VACCINE RABIDOG® (SAG2)

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As we are about to enter the 21st century, much progress has been achieved in the field of rabies diagnosis and control. Since the first vaccine made by Pasteur with a dried rabbit’s spinal cord, many safe and effective parenteral vaccines for human and veterinary use are available. Most of these veterinary vaccines such as RABIGEN® MONO (Virbac), derivate from the Pasteur virus strain, inactivated, and produced on cell line.

National massive dog vaccination campaigns are carried out in countries such as Mexico, South Africa, Thailand … where millions of dogs are injected yearly with rabies vaccine free of charge for the pet owner. Nevertheless, rabies is still present in these countries, as well as in many others in Africa, Asia, Latin America … Parenteral vaccination is not good enough as there are unreachable dogs – stray dogs or community dogs. For these dogs, an attractive oral vaccine combined to a pertinent action plan seems to be the solution to develop to eradicate rabies in the 21st century.

The development of an oral rabies vaccine for dogs was encouraged by the success obtained with oral vaccination of foxes in Europe. Indeed, in Europe, rabies came back in the 1960’s through the Eastern European countries. Infected foxes, unreachable by parenteral vaccination contaminated pets and domestic animals. Several methods were tried to stop its progression such as gazing of fox dens and night shooting, but these measures were unpopular and ineffective. Switzerland, as a pioneer country, developed the first oral vaccine for foxes. They later switched to Virbac’s RABIGEN® ORAL vaccine for safety reasons. After 20 years of oral vaccination, of which the last 8 years were with RABIGEN® ORAL, Switzerland became rabies free in 1999. In France, oral vaccination allowed containment of rabies in the north eastern quarter of the country only, and has now pushed it back to the German border. It has been mathematically proven that without oral vaccination, the number of rabies cases in France would not have stopped increasing to this day.

In France, oral vaccination of foxes is carried out by the use of helicopters. Each area is carefully selected on a map and precise routing is prepared. The product used contains the liquid SAG2 vaccine in a plastic blister coated by a special bait specifically designed for foxes: the bait flavor is fish (a very strong attractant). The bait contains a polymer enabling it to physically resist dropping from helicopters flying above 100 m high. The shape of the bait allows foxes to bite into the capsule, puncture it and ingest the liquid vaccine.

Due to the success of the bait-vaccine, a dog specific bait was developed: RABIDOG® ORAL in collaboration with CNRS, CDC, CNEVA, IRVT, Allerton Provincial Veterinary Laboratory.

The vaccine strain used is called SAG2. It is a live, attenuated, pure virus produced on cell line. It was selected by the use of monoclonal antibodies from the first oral vaccine used in Switzerland — SAD Bern. SAD Bern still has some residual pathogenic effect on mice due to the presence of arginine in position 333 of the envelope glycoprotein. The codon coding for this amino-acid was changed from AGA to GAA, thus with two nucleotid changes it is impossible for SAG2 to revert to the vaccinal mother strain. This double mutation leads to the replacement of arginine by a glutamic acid and is responsible for the loss of pathogenicity of SAG2 when administered to adult mice by the IC route. The innocuity of SAG2 was tested on more than 30 target and non target species including baboons, the most sensitive non human primates for rabies.

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Therefore, SAG2 has passed successfully the safety requirement recommended by WHO. This led to the signature of a “Memorandum of Understanding” between WHO and Virbac laboratories aiming at the development of oral vaccination of dogs in needing countries. The product developed for this purpose is called RABIDOG® ORAL.

Compared to the fox bait, it is very different and species specific:

- The shape of the bait allows an excellent prehension by dogs of all breeds and sizes.
- The flavor of the bait has also been changed to liver, more attractive for dogs.
- The SAG2 vaccine is lyophilized allowing better conservation in hot climates and storage at + 4°C (instead of – 20°C).

This also avoids discarding plastic blisters in the environment.

The coating of the bait is very thin, thus allowing the dog’s saliva to reconstitute the liquid vaccine within seconds, to put it in contact with oral mucosa and tonsils. However, it is thick enough to protect the bait.

The stability of RABIDOG® ORAL allows distribution under a temperature of 40°C during 5 days. Since distribution is done daily, we are sure to give an effective bait to the dogs in the street. Storage at +4°C can be up to 2 years.

Finally, the “chocolate” color of the baits has been changed to “cement / dirt” color so as not attract children’s attention. The smell of the bait is furthermore repulsive to man.

Dogs fed or unfed were showed to have 90 % acceptence of these baits within seconds.

Of course, the efficacy of SAG2 was extensively demonstrated in dogs in several experiments. SAG2 protects dogs against lethal challenges. It was also shown that the dog bait gave better results in dogs than the fox bait.

There is a difference in the monitoring of dog vaccination by seroconversion following oral and injectable vaccination due to different mechanisms of action of the vaccines: With injectable vaccination; we expect average seroconversion rates. With oral vaccination, these rates are different and the threshold of 0.5 IU/ml is not representative of protection. It has been shown when using the recommended effective titer of vaccine, that seroconversion can take more than 6 weeks and even not be detected. However, all protected animal showed an anamnestic response after challenge with a rabies virus (C. Rupprecht, CDC Atlanta). Anyway, since oral vaccination targets unreachable dogs, it is not possible to bleed them afterwards and monitoring of vaccination consists in counting the number of baits consumed.

The method of distribution of these baits should be adapted to each country’s situation. Three methods have been tested:

- central point distribution to pet owners
- door to door distribution
- wildlife model distribution (around garbage dumps)

All have advantages and drawbacks. Cost varies from one country to the other but oral vaccination of dogs will be cost effective compared to PET.

The first oral vaccination of dogs will start in South Africa in the Kwazulu Natal area. It is expected to increase the dog vaccination coverage in complement of parenteral vaccination as baits will handed out to “unreachable” dogs. Latin America and Asia will also develop this type of vaccination in order to eradicate rabies in the 21st century.