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The delivery of oral rabies vaccines to dogs: an African perspective

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ABSTRACT

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Dog rabies control relies principally on the mass immunization of dogs in order to achieve population immunity levels sufficient to inhibit rabies transmission. In Africa, such high levels of population immunity are rarely achieved due to a number of reasons. Oral immunization has been shown to be an effective means of inducing high levels of immunity in fox populations in several European countries, and this technique has been mooted as a means of overcoming the logistical problems of delivering injectable rabies vaccines to dogs. This paper discusses the requirements for oral rabies vaccines for dogs in Africa and reviews the trials performed to date on baits and baiting systems suitable for the delivery of such vaccines. Issues affecting possible rabies vaccine distribution in the future are discussed and the major research issues still to be tackled are summarized.

INTRODUCTION

Dogs are kept and tolerated at high numbers in most human societies. Cultural practices generally govern the level of supervision by humans of the social interactions between dogs and the access dogs have to resources such as food and shelter. It is assumed that high population densities of dogs permit the occurrence of endemic canine rabies, but although clear relationships between population densities and disease transmission dynamics have been demonstrated for many infectious diseases (Anderson 1992), this is not very well documented in the case of rabies. We suspect that the disease can be maintained by dogs alone, but that dog rabies may not always exist independently from wildlife rabies. There is, however, no doubt that rabid dogs are the major source of human infection. About 35 000 people die from dog-transmitted rabies worldwide every year. The vast majority of human cases occur in developing countries, where in some places the recorded numbers may exceed 0,5 cases/100 000 inhabitants/year (Bögel & Meslin 1990). The widespread occurrences of human rabies is due, not only to the frequency of exposures to rabid animals, but also to the failure to apply proper treatment to people bitten by rabid animals (Wandeler, Matter, Kappeler & Budde 1993). Dogs also create the necessity for the majority of treatments given after bite exposures. The number of people receiving post-exposure treatment for rabies is between 10 and 100 times greater than the number of recorded fatalities from the disease (Bögel & Motschwiller 1986).

The ultimate objective of rabies control is the protection of humans from infection and from economic losses. The occurrence of rabies in humans can be

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controlled by prophylactic (pre-exposure) vaccination and post-exposure treatment, by reducing the risk of human exposure, and definitively by disease elimination. In some areas it might be more cost-effective to bring dog rabies under control than to treat people bitten by potentially rabid animals. Rabies elimination programmes have to take into account not only the epidemiology of the disease, but also the biology of the target species. If the target species is the domestic dog, cultural constraints imposed by the human population have to be considered (Wandeler, Budde, Capt, Kappeler & Matter 1988). There are comprehensive guidelines developed by the World Health Organization (WHO 1984; WHO/WSPA 1990) for dog rabies control and dog population management. Both documents give detailed guidance on the planning and management of rabies control programmes, on legislation, and on tested techniques for use in local programme execution. Taking the costs and benefits of a campaign into consideration, we suggest that disease elimination should be the long-term goal rather than a temporary reduction in the rabies incidence rate. The most economical method of achieving this goal is by mass vaccination of dogs. Sustained national initiatives, rather than short-term local campaigns are essential if vaccination is to have the desired impact. Such programmes must have clear goals which take into consideration national structures and available resources.

Rabies elimination by oral immunization of animal populations is possible and this has been clearly demonstrated with respect to fox rabies in Europe. However, the technologies developed to control wildlife rabies in Europe and North America will need to be adjusted for dog rabies control and their delivery will require adaptation to African conditions. Concerns which need to be addressed when considering the oral immunization of dogs in Africa include vaccine efficacy and safety, the logistics of vaccine delivery and a thorough understanding of the epidemiology of dog rabies under African conditions.

Mass immunization methods have to be safe, simple and efficient, so that it becomes technically possible and economically feasible to establish the population immunity required to eliminate rabies (or inhibit its spread to uninfected areas). In many parts of the world, dogs are quite accessible for parenteral inoculation with safe and potent inactivated rabies vaccines and mass immunization campaigns of dogs have been successful in several countries (Larghi, Arrosi, Nakajata & Villa-Nova 1988; Wandeler *et al.* 1993). Unfortunately, more often than not the target level of immunization required is not attained (Bögel, Andral, Beran, Schneider & Wandeler 1982; Perry 1992). There are many reasons as to why the required population immunity in dog populations is not achieved, including inadequate logistics, insufficient community participation, large numbers of ownerless dogs, etc. It is often speculated that a majority of these problems could be solved with oral vaccines for dogs. Live attenuated and recombinant oral vaccines are presently being used to control fox rabies in Europe and Canada with considerable success (Wandeler 1991). However, the application of this concept to the control of dog rabies is not as simple a transition as it might seem. The oral vaccines and baits that immunize foxes very efficiently do not work well in dogs. Bait distribution systems for domestic dogs require approaches that are quite different from wildlife baiting. The logistic efforts required for their distribution may be as great as those required for a campaign using traditional parenteral immunization. Safety aspects will play a dominant role; the chances of human exposure to the vaccine are much higher than for oral immunization programmes directed at wildlife.

REQUIREMENTS FOR ORAL RABIES VACCINE DELIVERY IN AFRICA

The requirements for vaccines, baits and vaccine delivery systems for the oral immunization of animals against rabies have been presented and reviewed by a number of authors (Johnston 1975; Perry 1989; Wandeler 1991). As far as vaccines are concerned, efficacy and safety requirements have been addressed by international organizations (e.g. WHO 1988, 1989) and by national licensing authorities using such vaccines for wildlife rabies control. We repeat only the most important aspects here. At present only live rabies vaccines (attenuated or recombinant) fulfil the necessary efficacy criteria. There are marked species differences in the magnitude of the immune response following oral exposure to live vaccines and in the protection conferred. It appears to be relatively uncomplicated to vaccinate red foxes (*Vulpes vulpes*) by the oral route, whereas many other species require higher doses of vaccine for effective immunization. At present there are no vaccines available for the oral immunization of dogs under field conditions, although several candidate vaccines are under development. These include genetically engineered recombinants of pox- and adenoviruses bearing the rabies glycoprotein gene and carefully selected attenuated rabies viruses with reduced residual pathogenicity. Live virus vaccines for domestic dogs must meet higher safety standards than those presently used for wildlife rabies control, due to the close contact between dogs and humans. Ideally vaccines intended for oral immunization should be innocuous to humans, for the target species (even for very young dogs) and for other non-target species eating the bait. Unfortunately complete apathogenicity for all species (including immunocompromised individuals) may be an unattainable goal for any live virus vaccine. Lack of excretion of oral vaccines is another requirement which is difficult to fulfil completely.

If a safe, efficacious, and sufficiently thermostable vaccine becomes available, then an appropriate acceptable bait needs to be selected into which the vaccine can be incorporated. Important qualities of baits for selective vaccine delivery to dogs are that they are attractive to dogs but not to other species. In view of the potential residual pathogenicity of the vaccine to immunocompromised individuals, it is of utmost importance that baits are repugnant to humans. Baits must also be designed to maintain their integrity and attractiveness in the field for an appropriate time period. Once ingested, baits should permit the release of vaccine into the oral cavity, or deliver enterically-coated or acid-resistant vaccines into the small intestine. Clearly, optimal bait properties may need to be tailored to specific ecological and cultural conditions.

With appropriate vaccine and bait, the next requirement is a vaccine delivery system that assures mass immunization of domestic dogs. This necessitates the consideration of bait distribution strategies, including the bait densities needed for effective coverage and the frequency and mode of their distribution. It will be important to ensure the availability of adequate technical resources (such as vaccine storage facilities, vehicles, cold chain facilities), of administration structures and of manpower, as well as to take into account the constraints imposed by safety requirements, terrain, climate, land use system and culture.

REVIEW OF BAITING TRIALS FOR DOGS IN AFRICA

To date there have been very few trials carried out on bait delivery systems for dogs in Africa, and there are only four in the literature. Two of these were carried out in Tunisia and two in Zimbabwe, and they contrast markedly in the delivery systems studied.

The first trial to be carried out in the region was in Zimbabwe, where a technique analogous to that used to distribute baits to wildlife was evaluated in dogs in a Communal Land (Perry, Brooks, Foggin, Bleakley, Johnston & Hill 1988). The bait tested was a polyurethane sponge similar to one under evaluation at the time for raccoons in the United States (Perry, Garner, Jenkins, McCloskey & Johnston 1989). The sponge was enclosed in a heat-sealed sachet and filled with a placebo containing the biomarker rhodamine B. The bait was contained in a polyurethane bag to which was added a pungent offal-based attractant.

Three hundred and ninety six baits were distributed from bicycles in the Communal Land over an area of 60 km^2 estimated to support about 400 dogs. Bait uptake was evaluated the following day by inspection of dogs for biomarker staining when they were assembled at local cattle-dip tanks for annual rabies vaccinations. In addition, about 20 % of the distributed baits were retrieved and evaluated for signs of contact by biting.

About 25 % of the dogs presented for rabies vaccination showed evidence of bait uptake and about 80 % of baits examined showed evidence of contact. The authors commented that the high contact rates and relatively low uptake rates reflected a considerable underestimation of the dog population of the area, and thus a low bait:dog ratio. As 525 dogs were presented for rabies vaccination while only 396 baits had been distributed, the maximum potential baiting success would have been 75 %, assuming one bait for one dog.

This study was subsequently repeated in another Communal Land of Zimbabwe using a higher bait:dog ratio and a significantly greater bait acceptance rate of 72 % was achieved, as measured by the staining of dogs with the biomarker (Bleakley 1988).

The first Tunisian trial evaluated the uptake of a fishmeal polymer bait previously developed for the delivery of oral rabies vaccines to foxes in Germany (Haddad, Kharmachi, Schneider, Blancou, M'rabet, Ben Osman, Sassi, Douiri, Belhadj, Ben Salem, Messadi, Ben Hilled, Matter, Gritli & Turki 1989 cited by Kharmachi, Haddad & Matter 1992). Low bait uptake rates (in the order of 37 %) were reported. This led to a more extensive trial of four candidate baits tested in 200 dogs (Kharmachi *et al.* 1992).

Four baits were evaluated in which a biomarker (either rhodamine B or methylene blue), but no vaccine, was incorporated. In order to provide a comparison with the Zimbabwe trial, a similar polyurethane sponge bait with offal attractant was used and compared with three other baits; a sausage containing a plastic straw; a commercial fish meal bait with a paraffin wax-filled sachet; and chicken heads containing blister packs. Households were visited and each bait was given to 50 dogs. Bait uptake was observed at the time of administering the bait and by observation for biomarker after 2–3 hours.

Bait uptake rates, measured as a combination of those visibly accepted and those where significant biomarker staining was observed, were highest with chicken head baits (94 %), followed by fishmeal (62 %), sausage (26 %) and sponge baits (20 %). The authors commented that the low uptake of sausage baits were unexpected; they considered that this could have been explained in part by the rigidity of the straw inside, which became disassociated from the bait matrix and thus did not effectively mark dogs and in part by a poor response to the sausage bait itself.

These studies indicated that baiting systems can be used effectively for delivery of substances by the oral

route to dogs, even though success rates differed considerably depending on the system used. However, the polyurethane sponge bait, although useful as an inert medium for evaluating bait delivery systems, is not considered a suitable bait due to the difficulties in effectively containing vaccine in a sterile form. The chicken head bait, on the other hand, shows considerable promise. Kharmachi *et al.* (1992) commented that chicken heads are readily available and cheap in Tunisia as they are elsewhere in Africa, but drew attention to the labour intensity of attaching the blister-pack vaccine sachets to them by hand.

These studies investigated markedly contrasting delivery systems; direct presentation to individual dogs and non-specific indirect presentation by distribution from a vehicle. It is likely that both systems will be appropriate for certain circumstances in the delivery of oral vaccines to dogs, but neither is all-encompassing and a variety of delivery techniques should be considered if oral vaccines are to achieve their potential in the control or dog rabies (Wandeler 1993).

ISSUES AFFECTING POSSIBLE VACCINE DISTRIBUTION SYSTEMS IN AFRICA

If one accepts that the major constraints to effective dog rabies control in Africa are economic and logistical rather than technical (Perry 1993), then theoretically at least the use of oral vaccines provides a potential alternative or adjunct to the use of injectable vaccines in achieving higher rates of population immunity to rabies in dogs. However, when considering the translation of this theoretical concept into practice, numerous questions are raised in terms of the justification for using oral vaccines in dogs and the potential methods of their application.

What are the justifications for the use of oral vaccines in dogs in Africa? Three possible alternatives come to mind:

- to replace injectable vaccines;
- to "mop up" immunization of neighbourhood dogs; and
- to immunize selected "difficult" areas.

Considerable progress has been made recently on the technical issue of effectively immunizing dogs against rabies by the oral route (Rupprecht, Hanlon, Niezgoda, Buchanan, Diehl & Koprowski 1993; Schumacher, Coulon, Lafay, Bénéjean, Aubert, Barrat, Aubert & Flamand 1993) and although there are several hurdles yet to be overcome, it is probably only a matter of time before efficacious oral rabies vaccines for dogs are available on the market. Given the relative ease of administration and the possibility that dog owners, rather than veterinarians or veterinary assistants, could feasibly administer the vaccine, thereby potentially facilitating administration to a much larger proportion of the dog population, it seems likely that oral rabies vaccines could eventually replace injectable vaccines. However, it is probable that their initial field application will lie in the second and third alternatives, i.e. to 'mop up' immunization of neighbourhood dogs that are not presented for vaccination during rabies immunization programmes, a situation apparently common to much of sub-Saharan Africa, or to immunize selected areas that are inaccessible to traditional vaccination campaigns for geographical, logistic or social reasons. Examples of the latter could be the control of a rabies outbreak in an area affected by civil disturbance where government officials cannot operate effectively, or the control or rabies in dogs owned by transhumant or refugee populations.

What are the possible methods of distributing oral vaccines to dogs? These include:

- distribution as to wildlife species (either non-specific distribution, such as from a moving vehicle, or specific placement, without recovery, at selected sites);
- distribution to individual dog owners;
- distribution to dog owners through community leaders and extension agents.

As in the alternative justifications, these three methods are probably not mutually exclusive, but rather represent different circumstances and different temporal stages in the application of oral vaccine technology. In considering the choice of distribution method for a given set of circumstances, it is important to assess the comparative advantage of oral vaccines *versus* injectable vaccines. Of the three major logistical constraints to the effective control of dog rabies using injectable vaccines (accessibility of dogs to vaccination, availability of vaccine and cost of vaccine; Perry 1993) oral vaccines are likely to improve the accessibility of dogs to vaccination. Given the financial constraints affecting the delivery of government veterinary services in Africa, it will be important to ensure that oral vaccine delivery does not duplicate the logistical framework of parenteral vaccine delivery, and so maximum exploitation should be made of community participation in and administration of oral immunization programmes through the involvement of community leaders, health workers and extension agents. This is not without its difficulties as far as sustained motivation of the community is concerned. It is difficult enough in the delivery of primary health care to prevent prevalent infectious diseases of infants, but when considering rare (albeit highly fatal) diseases such as rabies, considerable attention will need to be given to the methods used to ensure sustainable adoption of oral immunization programmes by local communities.

SUMMARY OF RESEARCH NEEDS

The future research needs for the development of effective and sustainable dog rabies control in Africa using oral vaccines can be summarized under the following four headings:

Define the target populations

In the early stages of the application of oral vaccines in dog rabies control in Africa, they will likely be used as an adjunct to traditional injectable vaccines, enhancing access to dogs unavailable to traditional control programmes. These dogs include ownerless dogs and owned but poorly supervised dogs (Wandeler 1993). It will thus be important to determine what these sub populations of dogs are, how they can be identified and how they are most effectively accessed by oral vaccines.

Define the technical aspects of vaccine efficacy and safety

An oral vaccine for dog rabies control must be sufficiently thermostable and efficacious to immunize dogs under field conditions. Furthermore, safety requirements for oral vaccines for use in dogs must be much more stringent than for those used for wildlife immunization. Vaccines must be completely apathogenic for dogs and humans and for non-target species that may pick up vaccine baits. The live attenuated rabies strains SAD and SAG, and recombinant vaccinia and adenovirus vaccines all require high virus titres to immunize dogs by the oral route. All of them induce immune responses by infecting tissues (probably tonsils) of the oropharyx. However, if an effective way of avoiding the effects of high stomach pH can be found, vaccines that infect target tissues in the intestinal tract may be preferable particularly for safety reasons; such products do not exist yet. The use of the currently available live virus vaccines may not be feasible under circumstances where the risk of exposing severely immunocompromised humans is considered high. Genetically engineered vaccines with vectors incapable of replication are likely to be less hazardous. An adenovirus rabies-glycoprotein recombinant vaccine fulfilling this specification is currently being studied. Ideally, non-replicating (such as inactivated) rather than live oral vaccines are desirable, but immunization by the oral route with non-infectious vaccines is not currently possible and will only become so when technologies have been developed to allow an efficient transfer of non-replicating antigens through mucous membranes and their interaction with immunocompetent cells.

Currently available live attenuated and live recombinant vaccines are either too pathogenic or insufficiently proven for field application in dogs. If one of the presently available vaccines should be developed for field use in dogs, then a considerable amount of safety testing would be necessary. Differences in vaccine pathogenicity to different species are not always predictable. Vaccine innocuity should therefore be documented for all species that could possibly come in contact with it. The WHO now recommends that candidate vaccines be tested in immunocompromised primates and that target and non-target species be monitored for antibodies against viruses related to the rabies glycoprotein vector (WHO 1992; 1993).

Define the technical aspects of vaccine delivery

There have been very few studies of bait formulations, structures and attractants that make oral baiting systems suitable and specific for dogs under different circumstances in Africa. It would be desirable to replicate such studies in different areas of the continent to encompass the varying socioeconomic, cultural and climatic circumstances. Important in such trials is the standardization of techniques to allow comparison of delivery systems between studies and comprehensive guidelines for this purpose have been developed by WHO (WHO 1989, WHO/WSPA 1990). Worthy of specific mention is the need to include a reference baiting system in all trials carried out, although WHO does not specify what that reference system might be. Prime candidates as reference baits are dog biscuits (as used by Frontini, Fishbein, Ramos, Collins, Balderas, Quiroz Huerta, Gamel Rodriguez, Belotto, Dobbins, Linhart & Baer 1992 in Mexico) and chicken heads. In Africa, where the availability and formulation of dog biscuits varies considerably, there is a strong case in favour of using chicken heads, given their widespread availability, low cost and well-demonstrated efficacy as delivery vehicles of rabies vaccines to wildlife populations (Wandeler 1991; Bingham, Perry, King, Schumacher, Aubert, Kappeler, Hill, Aubert & Flamand 1993).

There still remains a general requirement to improve the capacity of baits to effectively release vaccines into the oral cavity.

Define the sustainability aspects of vaccine delivery

In countries with a highly-developed infrastructure, considerable economic resources and well-identified rabies reservoirs, it has been shown that rabies can be eradicated using oral vaccines in a relatively short time (e.g. Brochier, Kieny, Costy, Coppens, Bauduin, Lecocq, Languet, Chappuis, Desmettre, Afiademanyo, Libois & Pastoret 1991; Wandeler *et al.* 1988, 1991). However, in much of Africa it is likely that following their development, oral vaccines will only contribute, for the foreseeable future, to the better

control of rabies in dogs, rather than its elimination. This implies a sustained commitment to the successful deployment of such vaccines, due to the high turnover rate of dog population and the limited period of protection afforded by rabies vaccines. If oral vaccines are to exploit their comparative advantage, this will require a different approach to delivery of rabies control, with less emphasis on public sector provision of vaccination campaigns (constrained mainly by funding) and more emphasis on community participation. There are few examples of sustained delivery of animal health control measures through community participation in Africa, but possibly a parallel can be drawn with tsetse fly control. Successful control of tsetse fly, like rabies, requires either comprehensive public sector campaigns or sustained com munity involvement. Dransfield, Williams & Brightwell (1991) have demonstrated recently the feasibility of community managed tsetse and trypanosomiasis control in the Nguruman region of southern Kenya. Tsetse-transmitted trypanosomiasis is a recognized constraint to cattle production in the area. Control is based on local production and maintenance of impregnated targets for tsetse control, and the commercialization of wildlife and handicraft resources of the area to raise money for the control programme. Although the unique bond between the Masai and their cattle may provide an element of motivation for community involvement not present to the same degree in other livestock-owning communities and one possibly difficult to foster in dog-owning populations in rabies endemic areas, this study provides a pragmatic commercially-orientated approach that may have much wider application to other areas of animal disease control, including rabies.

But what are the ethical and professional issues affecting the wider provision of oral vaccines? Currently, parenteral vaccines are made available in many countries of the region through veterinarians, either government or private, and through pharmacies. Wider availability of oral vaccines to community leaders is theoretically desirable to increase vaccination coverage, but may be unacceptable to veterinary authorities for two reasons. Firstly, such authorities generally require that the use of biological products come under direct veterinary control and supervision (even though the widespread availability of parenteral rabies vaccines through pharmacies already compromises this). Secondly, there is an increasing trend in much of Africa to privatize veterinary services, and as such the devolvement of authority to use oral vaccines to allow their application by community leaders may be construed as compromising the future economic viability of privatized veterinary services.

Clearly, these issues need to be resolved before oral rabies vaccines for dogs become commercially available, to ensure their optimum use in the improved control and eventual eradication of rabies.

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