Rabies in vaccinated dogs: observations in eastern Nigeria

S.I. OBOEGBULEM*, M.I.O. OKOLO** and E.E. EROJIKWE*

Summary: Ten documented cases of rabies in dogs vaccinated with modified live virus (MLV) Flury-LEP vaccine in Anambra State of Nigeria between 1978 and 1985 are presented. The number constitutes 11% of laboratory-confirmed canine rabies, and suggests a vaccination failure rate of 2.5 cases per 10,000 doses of vaccine administered during the period. The interval between vaccination and clinical rabies ranged from six weeks to eleven months. Since the time and nature of exposure of the vaccinated dogs were unknown and the characteristics of the causative rabies viruses were not determined, it was not certain whether all ten cases represent immunity breaks or vaccine-induced rabies. All but one of the cases recorded involved human exposures. Probable causes and public health implications of immunity break and vaccine-induced rabies are discussed.


INTRODUCTION

Clinical records and epidemiological studies have established that, in Nigeria, the dog is the primary or maintaining reservoir of rabies, accounting for over 90% of animal cases (36, 37, 8, 23, 24, 15, 16, 26). Vaccination of dogs and cats is one of the important strategies in rabies control campaigns. The vaccines generally used in veterinary clinics are the modified live virus (MLV) avianized Flury strain manufactured by the National Veterinary Research Institute (NVRI), Vom. The Flury chicken egg vaccine compares favourably with tissue culture vaccines (32, 35). While vaccination has proved invaluable in prevention of canine rabies, absolute reliance can no longer be placed on it. Immunization with MLV vaccine is being hampered by increasing reports of vaccination failures and vaccine-associated rabies.

Post-vaccinal “immunity break” has been reported from many countries, including France (32, 31, 6), the United States (9, 18), Germany (41), Zimbabwe (19), Kenya (20), South Africa (3), and Tunisia (17). Several cases of vaccine-induced rabies in dogs and cats, particularly due to MLV Flury egg passage vaccines, have also been recorded. In the USA, three of five cases of rabies in vaccinated dogs in 1973 were observed after injection with live virus vaccine (10). Specifically, the Flury-LEP vaccines induced canine rabies with an incidence of 0.4 cases per one million; a higher incidence of 3 cases per million was recorded in the State of California (11).

* Department of Veterinary Pathology and Microbiology;
** Department of Veterinary Medicine, University of Nigeria, Nsukka, Nigeria.
From France, Placidi et al. (31) cited seventy-one cases of rabies in vaccinated dogs; nearly all the cases appeared within fifteen days of vaccination. Pedersen et al. (30) reported ascending paralysis in three dogs, which developed two weeks after inoculation with MLV Flury-LEP vaccine. The paralysis began in the inoculated limb. More recent cases of vaccinal rabies, discovered since the application of monoclonal antibodies, have been recorded (13, 14, 4, 5, 12, 34, 42).

In Nigeria, Bobade et al. (7) first reported death from clinical rabies of dogs duly vaccinated against the disease. Nawathe et al. (22) mentioned the case of a dog which a State Chief Veterinary Officer said he vaccinated annually for seven consecutive years and yet the dog died of rabies. In a retrospective analysis of case histories retrieved from laboratory requests submitted to NVRI, Okoh (28) documented fourteen cases of confirmed rabies in vaccinated dogs. The recorded cases represented dogs vaccinated in veterinary clinics variously located in northern and western States of Nigeria. In another report, Okoh (29) recorded clinical rabies in three vaccinated dogs in Vom, Plateau Area. This paper presents ten documented cases of confirmed rabies in vaccinated dogs in eastern Nigeria. Probable causes and public health implications of the apparent vaccination failures are discussed.

**CLINICAL OBSERVATIONS**

The case observations were made from clinical and laboratory cases presented severally to the authors and from data retrieved from veterinary records during a 10-year retrospective survey of rabies in Anambra State (25).

Although vaccine-induced antibodies will persist in dogs vaccinated with a single dose of the modified live Flury vaccine and may protect against natural exposure for up to three years (39), annual re-vaccination is officially recommended. Therefore, for purposes of this study, the effective duration of immunity for the NVRI vaccines is twelve months. Vaccinated dogs which died of rabies after twelve months post-vaccination, were not classified as cases of vaccination break.

There were ten well documented cases of clinical and confirmed rabies in vaccinated dogs in Anambra State between 1978 and 1985. Relevant case histories of the vaccinated rabid dogs, including date of vaccination, history of human exposure, date of confirmed diagnosis, and interval between vaccination and development of clinical rabies are presented in Table I. During the 8-year period, there were a total of 91 laboratory-confirmed canine rabies cases, although 264 cases were diagnosed clinically by field veterinarians (25).

The ten cases in vaccinated dogs thus represented 11% of laboratory-confirmed dog rabies. A total of 40,507 doses of anti-rabies vaccine (ARV) were administered to dogs in the State for the 8-year period (25), suggesting that 0.025% of the vaccine doses either failed to protect against natural exposure or induced vaccinal rabies. In other words, the vaccination failure rate is about 2.5 cases per 10,000 doses of ARV. The failure rate would definitely be much higher if all cases were fully documented, if duration of immunity were taken as three years, and if many more vaccinated dogs were naturally exposed to street rabies virus.
**TABLE I**

*Case histories: rabies in vaccinated dogs, 1978-1985*

<table>
<thead>
<tr>
<th>Case number</th>
<th>Form of rabies</th>
<th>Date of vaccination</th>
<th>Laboratory confirmation</th>
<th>Interval post-vaccination</th>
<th>Human exposure</th>
</tr>
</thead>
<tbody>
<tr>
<td>NS/RD78/3</td>
<td>Dumb</td>
<td>10-3-78</td>
<td>31-5-78</td>
<td>12 weeks</td>
<td>2 children bitten</td>
</tr>
<tr>
<td>NS/RD78/5</td>
<td>Furious</td>
<td>4-4-78</td>
<td>8-7-78</td>
<td>13 weeks</td>
<td>3 co-tenants of owner</td>
</tr>
<tr>
<td>NS/RD79/8</td>
<td>Furious</td>
<td>Early March 1979</td>
<td>15-8-79</td>
<td>5 months</td>
<td>Police inspector bitten</td>
</tr>
<tr>
<td>EN/RD79/3</td>
<td>Dumb</td>
<td>5-9-78</td>
<td>13-3-79</td>
<td>6 months</td>
<td>No history of human exposure</td>
</tr>
<tr>
<td>EN/RD80/3</td>
<td>Furious</td>
<td>6-4-79</td>
<td>3-3-80</td>
<td>11 months</td>
<td>Several persons bitten</td>
</tr>
<tr>
<td>EN/RD80/6</td>
<td>Furious</td>
<td>Dec. 1979</td>
<td>9-6-80</td>
<td>6 months</td>
<td>Owner and two other persons bitten</td>
</tr>
<tr>
<td>EN/RD81/7</td>
<td>Furious</td>
<td>June 1981</td>
<td>Aug. 1981</td>
<td>6 weeks</td>
<td>One person bitten</td>
</tr>
<tr>
<td>EN/RD84/2</td>
<td>Furious</td>
<td>Feb. 1984</td>
<td>Oct. 1984</td>
<td>8 months</td>
<td>Schoolgirl bitten</td>
</tr>
<tr>
<td>NS/RD85/4</td>
<td>Furious</td>
<td>Jan. 1985</td>
<td>31-7-85</td>
<td>6 months</td>
<td>Several persons bitten</td>
</tr>
<tr>
<td>NS/RD85/5</td>
<td>Dumb</td>
<td>Apr. 1985</td>
<td>19-8-85</td>
<td>4 months</td>
<td>Daughter of owner bitten</td>
</tr>
</tbody>
</table>

**DISCUSSION**

Clinical rabies in vaccinated subjects may be a result of immunity break or may be vaccine-induced. Vaccinal rabies is more likely to result from MLV vaccines insufficiently attenuated for the "target" animal species. Reports of several workers indicate that a presumptive diagnosis of vaccine-induced rabies may be made from the case history: a short interval between vaccination and onset of clinical signs; initial paralysis in the inoculated limb; prominence of the paralytic (dumb) form, especially in cats, absence of street rabies in the immediate area (14, 4, 42). Other reported biological characteristics of vaccine virus are: easy replication (adaptability) in embryonating eggs or cell culture; short incubation period in mice; absence of Negri bodies; and limited tropism for the salivary glands (4, 42). However, these characteristics and case histories are not definitive markers of vaccine virus strains (40, 42).

More recently, it has become possible to use monoclonal antibodies to differentiate rabies virus strains by their differences in nucleocapsid and glycoprotein antigens (43). This is a far more definitive technique for differentiating rabies viruses. A number of workers have used a panel of monoclonal antibodies to distinguish street virus and vaccinal virus, and to confirm vaccine-induced rabies in dogs and cats (13, 2, 14, 4, 42). Clinical observations in the present report are based solely on a retros-
pective analysis of available case records. It is not certain, therefore, whether all ten cases represent vaccinal rabies or immunity breaks. Vaccine-induced rabies is probable in some of the cases. In fact, the astonishingly high incidence of rabies in vaccinated dogs (11%) leads to the theory of vaccinal rabies.

Within four weeks after inoculation with MLV Flury-LEP vaccine, protective antibody titre is normally reached and the subject may be considered immunized. The probability that actual immunization has been accomplished is higher when an effective vaccine is administered by a competent person using an appropriate route to an immunologically responsive animal (33). Post-vaccinal immunity breaks may thus be caused by factors relating to (a) the vaccine, (b) vaccination procedure, and (c) the vaccinated animal.

The MLV Flury-LEP vaccines produced in Nigeria are considered valid for field distribution if the batch has a median mouse lethal dose (MLD_{50}) of not less than $10^4$ per 0.03 ml, or if the guinea-pig potency test shows that at least 70% of vaccinated guinea-pigs survive challenge (22, 27). In a study designed to monitor the potency of the vaccines in the field, Adeiga and Harry (1) titrated Flury-LEP vaccines sampled from six veterinary clinics. The viral titres obtained ranged from a mere 2% to 30% of the recommended minimum potency level. Reduction or loss of potency (resulting in vaccination failures) may be precipitated by environmental and other factors. Freeze-dried Flury vaccines should be stored for only one week at room temperature, one year at refrigeration temperature, and no more than one hour after reconstitution. The vaccines should be kept in a cool environment and away from direct sunlight. These recommendations are difficult to satisfy in actual field conditions in a tropical country—particularly where electricity supply is inadequate and unreliable, and where cold storage facilities are lacking in some veterinary clinics. Modified live vaccines have a lesser thermal stability since any drop in titre during a break in the cold chain leads to an uncontrollable drop in potency and since, once the vaccine is reconstituted, its conservation period is much shorter (2). Among the MLV vaccines, immunity failure seems to be associated more with the Flury egg passage vaccines (32, 31, 41, 6, 42). Owing to this relatively higher vaccination failure rate and the greater capacity to induce clinical rabies, the Flury-LEP vaccine is no longer licensed for marketing or recommended for use in dogs in many countries (11, 2, 4, 42). The inactivated cell culture vaccines are preferred and approved in these countries.

Immunity break may be attributed to incorrect administration of the vaccine, especially by incompetent personnel. To be effective, avianized vaccines without adjuvants must be given by the intramuscular route; if incompetently or inadvertently given subcutaneously, the vaccine becomes effective to the level of 30% only (38, 2). Intramuscular vaccination in sites other than the thigh has also been incriminated as a factor that diminishes vaccine potency and safety (9). Inadvertent sciatic or lumbar spinal nerve inoculation may precipitate vaccination failure or vaccinal rabies (4). Animal rabies vaccines should normally and legally be administered only by or under direct supervision of a veterinarian. However, veterinary students, livestock superintendents and even clinic assistants do often administer rabies vaccines in Nigeria.

Immune response of dogs to MLV avianized vaccines has sometimes been shown to be low, while some vaccinated subjects exhibit non-responsiveness. Immunity breaks arising from the vaccinated dog may be related to such host factors as age, breed, physiological status, and congenital immune deficiency (2, 6).
Adeiga and Harry (1) studied the antibody profile of 32 Nigerian dogs vaccinated with Flury-LEP vaccine and found that as much as 12.5% of the dogs failed to show measurable antibody response. The Nigerian dogs had a pool antibody titre of only 2.6 equivalent units per millilitre (EU/ml). Haddad et al. (17) found weak response in Tunisian dogs to antirabies vaccination. Immune reaction may be modified by climatic environment and immunosuppression may be caused by intercurrent infections or be induced by drugs such as corticosteroids (30, 2, 42). Blancou et al. (6) reported the case of a four-and-a-half year old bitch which contracted rabies, in spite of yearly vaccinations from the age of 3 years. Investigation revealed that the immune system was entirely deficient (hypogammaglobulinemia).

The phenomena of immunity breaks and vaccinal rabies have public health and epidemiological significance in Nigeria. Because minimal risk is assumed, owners and individuals exposed to vaccinated dogs or cats tend to have a sense of security that may be false or uncertain. Nine of the ten cases reported here involved human exposures. In at least two cases, the owners were reluctant to have their dogs confined, even when the daughter of a dog owner was exposed! In one case, the owner said he "saw no point" in taking his dog to a veterinary clinic when it was attacked by a stray rabid dog and when his dog bit two children because he had a valid vaccination certificate. He insisted the parents of the children could no longer hold him liable and wondered why immunoprophylactic treatment of the children was still considered necessary. When he was informed later that his vaccinated dog had died of rabies, the man expressed the view that our antirabies vaccinations are "meaningless" and "confusing". To minimize the confusion, there is need to apply the new technique of monoclonal antibodies to establish when a case of rabies is caused by a street virus or is vaccine-induced. The several cited references in other countries and the high incidence of rabies in vaccinated dogs observed in our report, support the theory of vaccinal rabies caused by the Flury-LEP strain. These observations underline the need to reappraise the continued production and use of the MLV Flury egg-passage vaccines in the country. Fortunately, a Vero-cell culture adapted Flury vaccine developed at NVRI has been satisfactorily tested and is awaiting WHO approval for commercial production (21, 22).

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RAGE CHEZ DES CHIENS VACCINÉS : OBSERVATIONS DANS L'EST DU NIGÉRIA.

Résumé : Les auteurs présentent dix cas argumentés de rage apparus chez des chiens vaccinés avec la souche vivante modifiée Flury-LEP dans l'État de l'Anambra au Nigéria entre 1978 et 1985. Ce nombre représente 11 % des cas de rage canine confirmés par le laboratoire, et traduit un taux d'échec vaccinal de 2,5 cas par 10 000 doses de vaccins administrées pendant la période considérée. L'intervalle entre la vaccination et l'apparition clinique de la maladie a varié de 6 semaines à 11 mois. Etant donné que la durée et la nature de l'exposition des chiens vaccinés étaient inconnus et que les caractéristiques des virus rabiques en cause n'ont pas été déterminées, il n'est pas certain que les dix cas soient dus à une rupture de l'immunité ou à une rage vaccinale. Dans tous les cas sauf un, des personnes ont été exposées à un risque de contamination. Les auteurs envisagent dans la discussion les causes probables ainsi que les conséquences de la rupture d'immunité et de la maladie vaccinale sur la santé publique.
RABIA EN LOS PERROS VACUNADOS: OBSERVACIONES AL ESTE DE NIGERIA.

Resumen: Presentan los autores diez casos argumentados de rabia que aparecieron en perros vacunados con la cepa viva modificada Flury-LEP en el Estado de Anambra en Nigeria entre 1978 y 1985. Representa esta cifra el 11% de los casos de rabia canina confirmados por el laboratorio, con lo que se pone de manifiesto un porcentaje de fracaso vacunal de 2,5 casos por 10 000 dosis de vacunas administradas durante el periodo considerado. El intervalo entre la vacunación y la aparición clínica de la enfermedad osciló de 6 semanas a 11 meses. Dado que se desconocían la duración y la índole de la exposición de los perros vacunados y no habían sido determinadas las características de los virus rábicos en causa, no es cierto que se deban los diez casos a una ruptura de la inmunidad o a una rabia vacunal. En todos los casos excepto uno, algunas personas estuvieron expuestas a riesgo de contaminación. Contemplan los autores en la discusión las causas probables, así como las consecuencias de la ruptura de inmunidad y de la enfermedad vacunal en la salud pública.


REFERENCES


