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# Post exposure human-prophylaxis for rabies in developing countries

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## Epidemiology

Three types of geographical categories of rabies exist:

(a) *areas free of rabies*, mostly islands: England, Australia, Japan and parts of the Caribbeans and Hawaii which require four to six months quarantine before any imported animal enters the country;

(b) *areas with controlled canine rabies but disease spread by wild animals*, e.g. western Europe (red foxes transmit to dogs, cats, deer); Canada (foxes and skunks); Caribbean Islands of Cuba, Puerto Rico, Hispaniola, Grenada and South Africa where mongoose rabies is found. In some areas of (a) and (b) aerosol transmission in laboratories, corneal transplant transmission and transmission by insectivorous bats have also been reported.

(c) *areas where canine and feline rabies continue*, e.g. in developing countries of Africa, India, Asia, Latin America [1]. In countries under (c), data on incidence of rabies – post exposure prophylaxis (PEP) unlike in developed countries [2] are often difficult to obtain, but the recent work of Bogel and Motschwiller [3] using 1979 analysed data showed varying rates of 0.1–28.8 per million cases of rabies and varying rates of PEP from South Africa to India.

**Table 1:** Human rabies, post exposure treatment

| Country | Population in Million | No. of Post-Exposure Treatment | | No. of cases of Human rabies | |
|---|---|---|---|---|---|
| | | Total | Per Million | Total | Per Million |
| * Algeria | 20.96 | 40,000 | 1908.4 | 50 | 2.0 |
| Argentina | 27.056 | 45,028 | 1996.9 | 6 | 8.2 |
| Bolivia | 5.5 | 2,575 | 468.2 | 6 | 1.1 |
| Brazil | 120.0 | 1,476.20 | 1230.2 | 148 | 1.1 |
| Colombia | 26.9 | 13,255 | 491.6 | 25 | 0.9 |
| * Ethiopia | 32.6 | 2,400 | 73.6 | 412 | 12.6 |
| India | 693.9 | 3,000,00 | | 20,000 | 28.8 |
| * Ghana | 11.6 | 31 | 2.7 | 21 | 1.8 |
| * Mali | 6.6 | 2,496 | 378.2 | 5 | 0.8 |
| * Morocco | 20.0 | 17,000 | 809.5 | 50 | 2.4 |
| * South Africa | 25.5 | 106 | 4.2 | 2 | 0.1 |
| * Sudan | 22.0 | 25,000 | 1136.4 | 25 | 1.1 |
| Thailand | 49.0 | 63,939 | 1304.9 | 370 | 7.6 |
| * Tunisia | 6.996 | 18,600 | 2658.7 | 20 | 2.9 |
| * Zimbabwe | 7.2 | 837 | 116.3 | 16 | 2.2 |

From data of Bogel and Motschwiller, *African Countries; (note Nigeria's data is unavailable).



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In this table, heavily populated Nigeria is conspicuously absent because accurate nationwide data are unavailable. Reports by Oduye and Aghomo[4] and Nawathe[5] reveal a high 1:5.8 ratio of human to dog rabies in Nigeria and yet many human rabies cases and dog bites remain unreported in Nigeria. Bite sites in humans include limbs, face and neck, and both adults and children are involved [6]. The work of Ezeokoli and Umoh [7] however confirms that Canine rabies rather than Sylvatic with dog-dog-human cycle prevails in Nigeria, and that suspected street rabies related isolates are not complicating classical rabies when tests with monoclonal antibodies were used. Such related isolates may have sero-epidemiological implications and could in future affect efficacies of classically based vaccines for PEP [8,9] and in Nigeria they include serotype 2 (Lagos bat virus) isolates from fructivorous bats, serotype 3 (Mokola strain virus) isolates from shrews and man and serotype 4 strains isolates from horses and mosquitoes[10]. A fatal human infection with Mokola virus has been reported in Nigeria[11].

### Zaria local PEP centre

Studies on clinical manifestations of rabies and applications of PEP were initiated in the early seventies in Ahmadu Bello Teaching Hospital by D.A. Warrell. In the later seventies and eighties, PEP and attempts at controlling the increasing menance of stray dogs have been adversely affected by deteriorating health care delivery facilities in Nigeria, absence of motivation from law enforcement agencies to enforce the leash law, making the purchase of human and dog vaccines and rabies antisera from foreign markets prohibited.

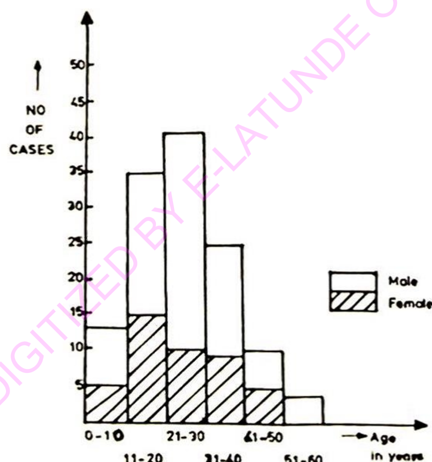


**Fig.1:** Dog bites in out patient department ABU Teaching Hospital Zaria (May 1983—March 1985)

Combined efforts by physicians and veterinarians were made in 1979 and 1985 to eliminate stray dogs. Analysis of dog bites from improperly kept records in out-patient department of Ahmadu Bello University, Zaria between (1983-1985) recorded 128 persons (87 males, 41 females) as bitten and all age groups were affected. Experience shows that many cases of dog bites in and around Zaria and other urban and rural centres in African countries are often unreported or treated at chemists shops or by traditional healers. Bite sites as recorded in out-patient records were leg and feet (37.3%), thigh (16.4%), upper limb (13.4%), trunk (2.98%), not stated (37.34%). Duration before presentation to A.B.U. Teaching Hospital, ranged between 1-42 days — such delays are caused by ignorance, not knowing where to go, delay in transportation etc. Twenty-nine (29) dogs were stated as traceable to owners, and 29 were stray. 7 were killed and their heads brought to hospital. Only 5 of the 29 dogs traceable to owners were up to date with routine vaccination. Anti-rabies post-exposure prophylaxis was given to 15 patients only as vaccines and antisera were generally unavailable, representing the scenario in most African countries. One case of clinical tetanus complicating a dog bite was recorded seven days post bite in a patient without PEP. Dog bites tended to be more rampant during the mating months of stray dogs. 14 cases of rabies deaths were found in the records since 1977.

### Knowledge, attitude and practice

In view of the important fact that cases of dog bites have to be treated by any doctor, a common questionnaire was administered to doctors from house officers to internists in different sub-specialities and also to final year medical students and the results are shown in Table 2. The outcome of this questionnaire underscores the great importance of improving the teaching and understanding of rabies in the curriculum of medical schools, primary health care workers, schools of nursing and schools of health technology.

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**Table 2**

| | | Final Year medical students (*n*=40) | Practising doctors (*n*=40) (1-8 years) |
|---|---|---|---|
| 1. | Can name 4 different types of rabies vaccines | 5% | 30% |
| 2. | Working knowledge of WHO criteria for PEP | 55% | 50% |
| 3. | Correct dosage of one named vaccine | 25% | 40% |
| 4. | Should direct uncooperative dog owners to police | 90% | 55% |
| 5. | Should educate dog owners on how to keep pets | 50% | 50% |
| 6. | Have you personally received anti-rabies prophylaxis | 0% | 0% |
| 7. | A puppy can be rabid | 20% | 35% |
| 8. | Knowledge of methods of diagnosis of rabid dog other than clinical and negri bodies | 10% | 15% |

**Exposure, WHO criteria and prevailing factors for PEP**

The attending physician must establish *exposure*, defined as penetration by teeth of rabid animal or contamination of scratches, abrasions, sprain, wounds, mucous membrane with saliva or body fluids of potentially rabid animal or rabid patient. Severe exposure includes bites of or licking of mucosa, abraded face, head, neck or fingers. Also it is noteworthy that clinical experience shows that puppies may be rabid; that a rabid dog may have dumb (paralytic) or furious rabies or may be healthy for more than the mandatory quarantine 10 days WHO period[10] while secreting rabies virus loaded in saliva persistently or intermittently—the so-called *chronic asymptomatic excretors*[11,12]. Ethiopian and Mexican street viruses were secreted by dogs up to 13 days or more before manifestation of clinical signs in the dogs[12].

Thirdly, the African clinician and veterinarian must cooperate and have improved access to reliable and rapid methods of diagnosing rabies in the biting animal in addition to mandatory quarantine services, viz: search for negri bodies in brain tissue, and recently in cardiac nervous tissue[13,14], mouse inoculation of isolates, fluorescent antibody technique staining (FAT) of brain impression smears and in cerebro-spinal fluid, rapid use of ELISA monoclonal antibody panel reactive against viral proteins; detection of virus in parotid gland, corneal smears, nuchal skin biopsy[15]; use of murine neuroblastoma culture[16] and indirect immunoperoxidase test and polymerase chain reaction for rabies[17]. Eleven out of 2191 FAT negative impression were positive by mouse inoculation and dot-blot detection of antigen at 20ng from canine parotid[15], stressing the importance of looking at false negatives.

The clinician, even when evidence of severe exposure is not available, may still safely use tissue culture vaccines as pre- prophylactic vaccine to allay anxiety and provide peace of mind in terrified and worried patients after dog bites. Thus WHO criteria can be modified in practice. Since survival after human clinical rabies is rare, and human trials with antiviral drug ribavirin[18] and antiviral therapy in mice and foxes[19] and intrathecal therapeutic use of live rabies RV 675 in monkeys[20] are all experimental, accurate diagnosis for instituting effective PEP remains the mainstay of prevention of



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rabies in developing countries.

**Ideal vaccine**

The ideal antirabies vaccine for the tropics should:

(a) elicit satisfactory neutralising antibody level (against viral glycoprotein of more than 0.5iu/ml by Centre for Diseases Control criteria;

(b) produce no or minor side effects;

(c) afford efficacious protection against clinical rabies;

(d) should be affordable within the health priorities of developing countries;

(e) should be compatible with rabies antiserum.

In the host defence against rabies in immunized subjects, neutralisation IgG titres against viral glycoprotein as well as T-cell recognition of rabies virus and possible generation of interferons and interleukin-2 are important[21,22]. From the originally isolated rabies virus which was adapted to rabbit brain in 1882 by Pasteur, variants are selected *in vitro* and cloned parental seed virus (CVS) are used for vaccine production throughout the world in Thailand, Japan, China, India, Europe and USA and Nigeria (where the Yaba vaccine was made until recently). Such vaccines made in animal brain, avian embryo cells or tissue culture cells are thereafter standardized by challenging mice immunised with strain of fixed virus usually distributed internationally from one stock but usually not with the locally available street virus[8]. Table 3 shows the types of vaccines currently available.

Inactivated virus keeps better under field conditions especially when lyophilized. Until 1953, rabies PEP followed the formula of daily injections with nervous tissue vaccine developed by Pasteur in 1885 while the WHO added hyperimmune serum which improved the outcome of severe rabid wolf bites in 1954 in Iran[1].

*The Semple vaccine*

This is produced by 5% saline emulsion of sheep brain infected with virus strain VP12 (inactivated with formalin), has variable potency and because it is cheap continues to be used in Asia and Africa. In 1:400 cases of Semple PEP, neurologic complica-

**Table 3**

| Nervous tissue type | Avian Vaccines | Tissue culture |
|---|---|---|
| I. *Adult animal brain* e.g. sheep, goats, rabbits Semple (phenol inactivated at 37°C) | (a) Duck embryo (B-propiolactone inactivated) | (a) Primary hemster kidney cell (inactivated Vnukoro-32 strain (PHKC) |
| | (b) Japanese quail embryo | |
| II. *Newborn animals* (a) Fermi type (phenol partially inactivated 22°C) | (c) Purified chick embryo fibroblast (PCEC) (Behringwerke); Flury low egg (LEP) passage strain | (b) French primary fetal bovine kidney culture (PBKCV) (Institut Pasteur) |
| (b) Suckling rats | (d) Purified duck embryo vaccine (PDEV) from Pitman-Moore strain virus | (c) Human diploid cell vaccine (Strain Wi 38) (Inst. Merieux) |
| (c) Suckling mouse (UV light or B-propriolactone inactivated. | | (d) Rhesus diploid cell |
| | | (e) Vero-cell line (verorab) |



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tions such as (major) – encephalitis, myelitis, meningitis, Guillaine-Barre's syndrome; (minor) — headache, myalgia, fever occur during 10th injection of 14-21 daily injections. T-cells reactive against myelin basic protein, cerebrosides and gangliosides GD1b and GT1b are the immunopathological basis of these complications which are more common in vaccines using adult animal brain. With suckling rat and suckling mouse vaccines, peripheral neuropathies are common[24]. These complications call for discontinuing the use of neural tissue vaccines in Africa.

*The Fermi vaccine*

This was reportedly used[25] in Egypt in 1987 on 21 patients severely bitten by rabid jackals (dosage 20 x 5ml daily injections). Three of the patients who subsequently died of rabies had low ELISA antiglycoprotein antibody levels of 0.7- 18iu/ml (protective ELISA antibody levels 20- 30iu/ml). The Fermi vaccine is thus not an ideal vaccine.

**Table 4:** W.H.O. PEP Procedure

**A.** Local treatment of wounds involving possible exposure to rabies. Recommended in all exposures.

(a) First aid treatment:

Immediate washing and flushing with soap and water, detergent or water alone is imperative. Then apply 40-70% alcohol, tincture or aqueous solution of iodine or 1% quaternary ammonium compounds with all traces of soap removed before applying quaternary ammonium compounds which can be neutralised by soap.

(b) apply antirabies serum by careful instillation in the depth of the wound and by infiltration around the wound.

(c) postpone suturing of wound and if suturing is necessary instill antiserum

(d) institute anti-tetanus procedure ATS, 1500 units after test dose sub. cut. and/or IM 0.1ml tetanus toxoid; and administer antibiotics and drugs (e.g. procaine penicillin) to control infections other than rabies.

**B.** Specific systemic treatment

| Nature of Exposure | Status of biting animal irrespective of previous vaccination | | Recommended Treatment |
|---|---|---|---|
| | At time of exposure | During 10 days (cats and dogs) | |
| 1. Contact; but no lesions. Indirect contact, no contact. | Rabid | — | None |
| 2. Licks of skin; scratches or abrasions, minor bites (covered areas of arms trunk and legs) | (a) Suspected as rabid | Healthy | (a) Start vaccine. Stop treatment if animal remains healthy for 5 days (proved negative by brain fluorescent antibody. |
| | (b) Rabid, wild animal or animal unavailable | Rabid | (b) Start vaccine; administer serum upon positive diagnosis and complete the course of vaccine. |
| 3. Licks of mucosa; major bites (multiple face, head, neck, finger) | Suspected rabid domestic or wild animal; animal unavailable | | (c) Serum + vaccine Stop treatment if animal remains healthy for five days. |



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Duck embryo vaccine (given as 21 doses) is imported into Nigeria and other developing countries and reports of its failure to prevent rabies by producing optimal neutralisation titre despite combined rabies immune globulin have been documented [26]. This confirms the poor antigenicity of unpurified duck embryo vaccine, and studies show that adverse reactions are numerous viz; neurological, including headaches, photophobia, paraesthesiae, listlessness, transverse myelitis, cranial nerve palsies; bronchospasm and regional and generalized lymphadenopathy and systemic anaphylaxis. Patients with previous egg proteins allergy, dysgammaglobulinaemia, previous use of avian vaccine (eg. yellow fever, influenza) are predisposed while combination of duck embryo vaccine with equine serum increases [27] the prevalence of serum sickness in children (16%) and adults (43%).

Efforts to purify chick embryo vaccine by Behringwerke by removing chicken protein and neuronal tissue from vaccines made from flurry low egg passage (LEP) virus strain has produced freeze dried purified chick embryo cell vaccine (PCEV). This vaccine has been tested in *intramuscular regimens* on days 0, 3, 7, 14, 30, 90 in volunteers [28] and found to produce adequate antibody titre 0.51 iu/ml at 14 day. Multisite intradermal low dose regimen has recently been found to produce effective antibody titres in Thailand [29]. Thus purified duck embryo vaccine should be used in African countries.

*Tissue culture vaccines*

The WHO recommendation for cell culture vaccines is that 1ml should be given into the deltoid intramuscularly on days 0, 3, 7, 14, 28, 90 and combined with 20 iu/kg of human rabies immunoglobulin for severe PEP. Various research works have pointed to modification of this recommendation.

*Fetal bovine kidney cell vaccine* (FBKCV – Institute Pasteur

This vaccine has been found on day 14 to have more than 1iu/ml (Enzyme immunoassay Inst. Pasteur) with geometric mean of 3.38 (range 1-32 in 126 of 141 vaccines while on day 45, 128 out of 130 had geometric mean titres of 11.52 range 2-32) [30].

*Primary hamster kidney cell rabies vaccine* (PHKC)

Made from Beijing strain of fixed virus grown in hamster kidney cells, it has been tested as (a) plain vaccine given 2mls subcutaneously from day 0 to 14 daily (b) vaccine with adjuvant 2mls subcutaneously or intramuscularly on days 0, 7, 14 (c) as concentrated PHKC given 1ml intramuscularly on days 0, 3, 7, 14 and (d) as concentrated with adjuvant and given 2mls intramuscularly on days 0, 7, 14. Mild reactions occurred in the (b) regimen which were worsened if injections were extended to days 24 and 34 and dizziness, fatigue and lymphadenitis supervened. Potency of Habel index of more than $10^4$ were obtained with each regimen and all were compatible with equine serum 0.5ml/kg intramuscularly [31].

*Human diploid cell vaccine* (HDCV)

The combination of HDCV introduced in 1974 and equine rabies antiserum was tested in 45 severely bitten patients in Iran between 1974 and 1976 and since none died [32], had become the cornerstone of PEP in USA and Europe where equine rabies antiserum has been replaced by the much safer but more expensive human rabies immune globulin (HIG). WHO has recommended 5 or 6 injections intramuscularly on days 0, 3, 7, 14, 28 and perhaps 90 day. The 90 days booster has been recommended for both HDCV and concentrated purified duck embryo vaccine (PDEV, Berna 2.5-4.5 iu antigen per dose) since 25-38% of persons tested after 5th dosage before 90 day have been found to have antibody levels below 0.5iu/ml [33]. A report [34] of rabid mongoose bite treated with HDCV x 5 doses and HIG resulted in death on 37th day before the sixth dose could be given.

It is important for the physician to recognise and avoid adverse factors which can result in HDCV vaccine failure viz: (a) administration into gluteal region where fat may trap the vaccine, the deltoid in adults or anterolateral thigh muscles in children are preferable [35], (b) concurrent administration of chloroquine [36] which is immunosuppressive at the concentration of 12-25mg per ml *in-vitro* (c) administration of all intramuscular doses in one arm [37] (d) during the first seven days of HDCV and HIG, less antibody is available in the blood of the vaccinee when 20 iu/kg rather than 30-40 iu/kg of HIG is given and if larger excessive doses of HIG are given it becomes immunosuppressive [38, 39] (e) concurrent use of immunosuppressive drugs, steroids, ACTH [40] and concurrent underlying infection and failure of the cold chain all result in ineffective vaccination [41].

**Testing for HDCV in Nigerian students**

In children, aged less than 4 years given 0.5ml subcutaneous HDCV dose and 1ml of HDCV in children more than 4 years old[42], appropriate adequate antibody titres are induced. A previous report of de-

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creased antibody response in persons from less developed countries [43] e.g. Kenya after pre-exposure vaccination with HDCV prompted us (Onyemelukwe and Ogunkoya) to vaccinate medical and veterinary Nigerian students to determine their seroconversion to intradermal 0.1ml HDCV (lot $V_o$ 456 antigenic value 3.41 iu/ml Merieux Instit Lyon France) prepared from Wistar Institute Pasteur derived Pitman Moore – 1503-3n strain of rabies virus grown in MRC-5 human diploid cell and inactivated with betaproproleactone. 0.1ml intradermal injections were given on days 0 and 14 and the students were bled before the first injection and on day 10. Serum samples stored at $-20^{\circ}C$ were transported to CDC Atlanta, Georgia, U.S.A. where they were diluted five fold and tested by fluorescent focus inhibition test (RFFIT) [43]. Table 5 shows the results of 13 of 27 students (age range 17 – 29) who completed the study. USA public health considers a titre 1:16 adequate for pre-exposure prophylaxis while WHO considers 1:50 or 0.5 iu/ml as adequate anitbody titre at day 14.

Four students had 1:5 titre, 6 had 1:25 and 3 had 1:125 titre on result which shows variable response in these Nigerians to HDCV; All the students had no significant pre-vaccination antibody levels hence were predisposed to rabies. There is thus a need to evolve strategies for effective vaccination. Turner *et al* [44] in studying 194 volunteers with 1ml IM and 0.1ml id dosage 28 days apart suggested that post exposure non-severe prophylaxis could be adequate with either regimen. Our results show that after two 0.1ml id pre-exposure vaccination of Nigerian students, further boosters are necessary.

**Early antibody responses to rabies vaccines** (tissue culture vaccines)

The aim of post-exposure rabies vaccine treatment is to induce immunity as fast as possible, measured as neutralising antibody. During the seven or more days between giving the first dose of vaccine and the appearance of detectable antibody, the patient has no specific immunity to rabies virus. Simultaneous passive prophylaxis with hyperimmune serum is given to cover this period (at dose 30-40 iu/kg HIG) but in tropical rabies endemic areas the prohibitive cost of hyperimmune globulin often leaves this vulnerable period uncovered. Turner [45] first showed that 0.1ml given intradermally at multiple sites induced antibody by day 7. Nicholson *et al* [46] showed that eight-site id vaccination on day 0 gave faster results than conventional IM regimen. The recent study of Suntharasami *et al* [47, 48] in Thai subjects using six different regimens and two tissue culture vaccines (HDCV and Vero cells rabies vaccine (PVRV) confirmed that no antibody was detected before day 5 by any regimen while titres less than WHO protective level of 0.514 per ml was detected at day 17 in 25 of 118 patients. All subjects irrespective of the regimen used had antibody at day 14. HDCV is a poor interferon inducer [49] and various regimens [50, 51, 52, 53] have been researched.

**Table 5:** Antibody response in Nigerian students to HDCH

| | *Sex* | *10/7/85* | *2/8/85* |
|---|---|---|---|
| 1. | M | ∠ 1:5 | 1:25 |
| 2. | M | ∠ 1:5 | 1:125 |
| 3. | M | ∠ 1:5 | 1:5 |
| 4. | M | ∠ 1:5 | 1:25 |
| 5. | M | ∠ 1:5 | 1:5 |
| 6. | M | ∠ 1:5 | 1:125 |
| 7. | M | ∠ 1:5 | 1:25 |
| 8. | M | ∠ 1:5 | 1:125 |
| 9. | M | ∠ 1:5 | 1.25 |
| 10. | M | ∠ 1:5 | 1:25 |
| 11. | M | ∠ 1:5 | 1:5 |
| 12. | F | ∠ 1:5 | 1:25 |
| 13. | F | ∠ 1:5 | 1:25 |

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**Table of regimens with vaccines** (Suntharasami *et al*, 1987)

| *Vaccine* | *Routine Vol.* per site | | *Days and number of sites* Day 0 | Day 3 | Day 7 |
|---|---|---|---|---|---|
| 1. HDCV | IM | 1 | 1 | 1 | 1 |
| 2. HDCV | IM | 1 | 2 | 2 | |
| 3. HDCV | IM | 1 | 3 | | |
| 4. HDCV | id | 0.1 | 8 | | 4 |
| 5. HDCV | id | 0.1 | 4 | 4 | 4 |
| 6. HDCV | SC | 0.25 | 8 | | 4 |
| 7. PVRV | IM | 0.5 | 1 | 1 | 1 |
| 8. PVRV | IM | 0.5 | 2 | 2 | |

Therefore human or equine hyperimmune rabies immunoglobulin must be given within the seven days vulnerable period and not later when further antibody suppression may occur. Current vaccines are poor interferon inducers in humans even when started on first day of bite; the window period of seven days should be additionally covered with oral or parenteral use of interferon inducers like saponins [53] or trial use of human recombinant interferon (KEMRON) in severe face and neck bites of proven rabid animal while passive ERIG, HIG and active vaccination are instituted where financial constraints are not prevailing problems.

## Cost-effectiveness and alternative vaccine regimens for African countries

The decision to embark on PEP in a developing country should be an informed decision based on degree of exposure, the rabies potential of the biting animal, psychological disturbance of the patient; the availability of what type of vaccine (cost, efficacy, safety) and its rational economic use, the availability or not of human immune globulin (HIG), equine rabies antisera (ERAS) or purified equine rabies immunoglobulin (ERIG) and the possibility of compliance with follow-up.

### A. Single Regimens

I. WHO/Conventional manufacturers regimen (Each HDCV vial is 1 ml and where finance is available)

| | 1 | 1 | 1 | 1 | 1 | 1 |
|---|---|---|---|---|---|---|
| Day | 0 | 3 | 7 | 14 | 30 | 90 |
| Dose | 1ml | 1ml | 1ml | 1ml | 1ml | 1ml |

1ml IM or subcut. with HIG 20-40iu/kg given.

II. Turner *et al* regimen [44, 45]

(a) For non-severe post-exposure prophylaxis (not head or neck or deep wound) for persons with clear history of measured seroconversion of 0.5ml iu/ml prior to exposure, 2 injections of id 0.1ml was found to induce antibody two fold lower than for 1.0ml IM dose but still effective antibody titres.

| 1st | 2nd |
|---|---|
| Immediate<br>1ml IM<br>or<br>0.1ml id | 10-20 day<br>1 ml IM<br>or<br>0.1ml id |

These workers also recommeded pre-exposure prophylaxis where exposure is low (customs, veterinary students) of 0.1ml id or 1.0ml IM at day 1 and repeated 28 days later with or without booster at 2 years.

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(b) For severe post-exposure prophylaxis in patients with previous inoculation with HDCV of proven immunogenic value (2.5ng) whose serum neutralising antibody value has not been determined, Turner *et al* suggested the following regimen

| Day | 0 | 10 | 20 | 90 |
|---|---|---|---|---|
| Dose | 0.1ml id OR 1ml IM | 0.1ml OR 1ml | 0.1ml OR 1ml | 0.1ml OR 1ml IM |

In addition to health education of patients and vigorous wound cleaning, group I WHO patients with no contact could receive pre-exposure prophylaxis of 0.1ml id on day 1 and repeated on day 10, to assure their peace of mind.

III. Haverson's single site (HDCV) low dose regimen [54]
Haverson proposed this regimen as most appropriate in developing countries if one vial of HDCV only is available.

| Day | 0 | 3 | 7 | 14 |
|---|---|---|---|---|
| Dose | 0.1ml id | 0.1ml id | 0.1ml id | 0.1ml id |

The earliest antibody assessment of this regimen was 13-45 days after vaccination. With this regimen, 328 patients followed up for one year did not develop rabies and no HIG which is expensive was given. However, accurate intradermal placement of the vaccine is very essential for this low dose regimen.

**B. Multisite HDCV Regimens**

I. Kenyan multisite (HDCV) intradermal regimen (Rees *et al*) [55]
On first day two to four multiple sites are used, and single site subsequently.

| Day | 0 | 2 | 4 | 6 | 13 | 29 |
|---|---|---|---|---|---|---|
| | 0.1ml x 2 sites OR 0.1ml x 4 sites | 0.1ml | 0.1ml | 0.1ml | 0.1ml | 0.1ml |

At least three follow-up intradermal injections are necessary if the whole cannot be completed. HIG if available is given if short incubation is anticipated, or if initiation of treatment is delayed, or if possibility of inadequate immune response is seriously suspected.

II. Warrell's multisite (HDCV) intradermal or subcutaneous [50] low dose regimen
During the first two injection periods, multiple sites are used in this regimen. Antibody was detected within seven days of first dose and from 14 day all groups showed excellent antibody (above 0.5iu/ml) response. The possibility of suppression of antibody by giving HIG was prevented by giving the second dose not later than day 7 instead of day 14. Accurate intradermal injection is essential but increased volume is needed if subcutaneous route is employed. When 8 sites are used, injections are given into the deltoid, suprascapular, thigh and lower abdominal wall regions, and for 4 sites, injections were given into the deltoid and thigh areas to maximize involvement of numerous groups of lymph nodes in the immune response. The use of vaccine alone was found superior to continuing with adjuvants (aluminum hydroxide) as local pain, itching, headache and mild fever and lymphadenopathy were seen more in those who received vaccine with adjuvant. It is obvious that multiple pricking of the skin in children is a disadvantage as well as a cause of loss to follow-up even in adults.

(a)

| Day | 0 | 7 | 28 | 90 |
|---|---|---|---|---|
| | id 0.1ml x 8 sites | id 0.1ml x 4 | 0.1ml x 1 | 0.1ml x 1 |

(b) For restless children and thin-skinned elderly people 0.25ml HDCV subcut. x 4 with 0.1ml aluminium hydroxide.

| Day | 0 | 7 | 28 |
|---|---|---|---|
| | Sub 0.25ml x 4 sites | 0.25ml x 2 sites | 0.25ml x 1 site |

The 8 site id regimen has been tested and it was found that, two years after use in 70 patients, no patient had died.

The use of intradermal low dose HDCV in Haverson's regimen, Kenyan regimen and Warrell's regimen reduces the cost of syringes, cost of hospital



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visits and HDCV vaccine when compared to WHO conventional course of Merieux HDCV cells for 5 doses during the first month. Warrell's regimen incorporates 66-78% reduction in costs while Haverson's regimen is even cheaper. Purified Vero cell rabies virus (PVRV) costs less than HDCV and could replace HDCV in low dose regimens.

(c). Alternative low dose regimen based on purified chick embryo cell rabies vaccine (PCECV) — multisite intradermal regimen. Suntharasmai and co-workers [48] have assessed multisite use PCECV which is 30% cheaper than HDCV. Their intradermal multisite (4 and 8) injections on days 0, 7, 28 produced similar antibody responses to intradermal multisite regimen of Warrell. Few side effects of site irritation and induration (3 in 177 patients) had been reported for PCECV. Concomitant use of passive anitbody with PCECV showed that, in the patients given HIG with PCECV, increased neutralising antibodies were found on day 7, while with equine heterologous antirabies serum (EARS) increases were not obtained. Both HIG and EARS suppressed later antibody responses but not to levels that would jeopardise prevention of rabies. EARS also caused generalised reactions in three patients however, indicating the risk involved with use of unpurified equine anti-rabies serum.

**Passive antibody rabies immunisation for developing countries**

The WHO recommendation for severe PEP with cell culture vaccines is 20 iu/kg of human rabies immunoglobin. Reports have shown the importance of use of either duck-embryo vaccine or human diploid vaccine simultaneously with rabies immunoglobulin after rabid bites, but failures of protection have occurred due to long delays before therapy and sub-optimal neutralising antibody [41]. Mertz and co-workers [38] demonstrated that 20 iu/kg of HIG could not sustain antibody levels of 0.1iu/ml or more by 7 day, hence, the recommendation of 40iu/kg, while excessive amount of passive antibody which could suppress host antibody response should be avoided. The study of Wilde *et al* [56] has shown that unpurified equine rabies antibody may be associated with allergic manifestations while purified equine rabies immunoglobin (Pasteur ERIG or SWISS ERIG) given as 40 iu/kg was associated at days 6, 7, 10, 12 with mild reactions in only 4 out of 485 cases. It is stressed that if skin testing with 1:10 dilution of ERIG raises a bleb of 5mm or more, ERIG could still be given after oral antihistamines. Since ERIG is cheaper than HIG and fairly safe [56], it should displace unpurified (EARS) antiserum in combination with intradermal low dose tissue culture vaccination regimens. These low dose tissue culture regimens outlined above have been found to generate protective antibody levels of above 0.5 iu/ml by day 7 and ERIG passive prophylaxis should protect the early window period before active vaccination elicits protective antibody.

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