

Rabies Vaccine

Several readers have expressed the need for updating and have sought clarifications in , relation to rabies vaccine. In this context,. Dr. T. Jacob John, Professor and Head, Department of Clinical Virology, Christian Medical College Hospital, Vellore, Tamil Nadu 632 004 continues answering some important questions. Professor Jacob John, the current Chairman of the IAP Committee on Immunization, is a leading International Vaccinologist and an Adviser on Immunization to the World Health Organization and other International Agencies.
Editor-in-chief

Q 1. Should dog bites be classified into Classes I, II and III before giving rabies vaccine?

A 1. When only animal-brain rabies vaccine was available, we were worried about the possible adverse reactions to the vaccine and had to weigh the risks and benefits of rabies vaccination very carefully. The probability of the demyelinating reaction is determined partly by the amount of myelin proteins injected. One therefore, liked to give as low a total dose of the vaccine as possible. On the other hand, the protective efficacy was determined by the total amount of virus antigen given hence one liked to give a larger total dose. To resolve this opposing forces, a system was developed to classify animal bites into 3 classes in order to choose from 3 graded dosage regimens. For lowest risk, namely Class I, the least amount of vaccine (*e.g.*, 2 ml x 7 days) and for highest risk, namely Class III, the highest amount of vaccine (5 ml x 10 days) would be prescribed. For intermediate risk (Class II), an intermediate amount of vaccine (*e.g.*, 3 ml x 10 days) would be given. It was for this reason that the bites were classified as Classes I, II and III.

This system of classification is no

longer relevant when the safe cell culture vaccines are prescribed. However, as stated earlier, the bites should be assessed from the point of view of risk of rabies virus inoculation, before immunoprophylaxis is prescribed. The World Health Organization (WHO) recommends to assign animal bites into 2 categories, namely those without risk and those with risk. No immunization need be given when there is no risk. When there is risk, both passive and active immunization are recommended by WHO. In India, such a practice will increase the demand for anti-rabies serum (ARS) or human rabies immunoglobulin (HRIG) for passive immunization and for the vaccine itself for active immunization. Due to insufficient supply of ARS and HRIG as well as due to the very high cost of HRIG, and also partly due to the relatively high cost of the vaccine itself, we should somehow use a rational system to reduce the consumption of both these modalities. For this reason I have recommended a risk-assessment scheme which has a different function than the old classification scheme. Before prescribing the course of prophylaxis after a dog-bite, a decision-tree should be followed, based on risk assessment. Details of the risk assessment scheme will be presented later.

Q 2. *How is risk analysis made in a case of dog-bite?*

A 2. A risk analysis approach for decision making for a person who had not been previously immunized, is given below. Since the process has sequential branching, the term "decision-tree" is applied to such algorithms. .

Reported dog bite: If the wound was not cleaned thoroughly with water and soap, do that before proceeding further. Take detailed history.

Examine carefully; use a hand-lens if necessary.

Step 1. Is skin broken?

If no, there is no risk.

If yes, go to Step 2.

Step 2. Was the dog fully immunized? If yes, there is no risk. If no, go to Step 3.

Step 3. Was the dog behaving normally? If no, there is risk. Offer passive and active immunization. If yes, go to Step 4.

Step 4. Was the bite provoked?

If no, suspect abnormal behavior. For bites on head, neck, hands or genitalia give passive and active immunization. For all other sites, commence active immunization with vaccine on days 0 and 3 and go to the next question in Step 5.

If yes, probably there is no risk; however, risk has to be further assessed by the behavior of the dog, if the dog is identifiable and available. In order not to lose time, commence immunization with vaccine on day 0; and go to the next question, in Step 5.

Step 5. Is dog available for observation for the next 10 days?

If no, review the answer to the question in Step 4. For unprovoked

bite on sites other than head, neck, etc., continue vaccine on days 7, 14 and 30. For provoked bite, proceed exactly as if bite was unprovoked. If yes, (i.e., dog is available for observation), review Step 4. For unprovoked bite on sites other than head, neck, etc., consider the condition of dog on every day until day 7. If dog is well, postpone the third dose to next day; if dog is well on day 8, postpone to day 9; if dog is well on day 9, postpone to day 10. If dog is well on day 10, offer third dose one month later as "pre-exposure" type of immunization. Give a fourth dose 3 to 12 months later.

For provoked bite on sites other than head, neck, etc., review dog's health on daily basis. If dog remains well for 10 days then give second dose one month and third dose 3-12 months later. For provoked bites on head, neck, etc., give vaccine on days 0 and 3 and review dog's health on daily basis. If dog remains alive for 10 days, continue as for pre-exposure immunization.

If dog becomes sick or dies upto day 7, then immediately give passive prophylaxis with ARS or HRIG, thus converting the prophylaxis to passive and active immunization. This should be applied both for provoked and for unprovoked bites on any site. If dog sickens or dies on day 8, 9 or 10 immediately give the third dose of vaccine (dose for day 7) and then continue with the next doses on days 14 and 30.

Note: When reading for the first time, the decision-tree may look very complex. In practice, however its application is relatively easy. It is important to remember not to down-grade dosage schedule for any assessed level of risk; if considered prudent, one can up-grade the dosage schedule, particularly if the client so wishes.

Q 3. Many doctors advise to keep the biting dog under observation for 10 days. Only if the dog dies do they prescribe rabies immunization. Is this scientifically correct?

A 3. This approach may be adopted in certain limited circumstances, but it is in general a risky procedure. Suppose that a dog was kept under observation after it bit some one. On the seventh day it became sick and on the ninth day it died. Under these circumstances, rabies immunization would be commenced either on day 9 or the earliest on day 7. However, rabies virus had been inoculated on day 0. Thus several precious days have been lost in this process. Now, on day 7 there is no choice but to give immediate passive immunization followed by active immunization, on days 7, 8, 9, 14, 30 and 90 and hope for the best. If, on the other hand vaccine doses had been given on days 0 and 3, then the next dose would have any way been due on day 7, at which time the person would have begun producing antibody.

In case the bite had been on head, neck or hands, the 7 days of delay in immunization could become a fatal mistake. According to the decision tree, if the bite was unprovoked, then passive immunization would have been given to the person on day 0 itself. Had the bite been provoked, then doses would have been given on days 0 and 3. Then if the dog became sick on day 7, the situation would be re-assessed. On day 7, I would give passive immunization especially for bites on sites such as head, neck, hands or genitalia and then continue with the active immunization, by giving vaccine on days 7, 14, 30 and 90. Under such circumstance I would give passive immunization only upto day 7; thereafter I would not give passive immunization, since 3 doses of vaccine would have been given anyway by day 7.

Irrespective of the site of bite, whenever possible, the biting animal should be kept under observation for 10 days. In case the animal is obviously sick at the time of bite, it should be killed in the most humane way, which is by giving an overdose of an anaesthetic. For this the help of a veterinarian should be obtained. In case the dog is not owned (stray dog) then it should be captured by roping and then killed by proper experts. Beating dogs to death is inhuman.

Q 4. Does human-to-human rabies virus transmission occur? Do health care workers and family members who handle rabies patients require immunization?

A 4. Unlike the dog's saliva, human saliva of rabies-affected persons seldom contain detectable rabies virus. I have personally examined saliva from 50 patients with rabies and did not find rabies virus in any of them. However, virus in the saliva has been detected by other investigators. For these reasons the risk of rabies virus transmission from person to person is very low indeed. Although there is the common hearsay that persons with rabies bite like dogs, there is no truth in it at all. Thus, neither health care workers nor family members are at any real risk of rabies infection. However, when medical interventions (suctions, venipuncture, tracheostomy, biopsy, etc.) are made, there is always an element of risk; hence precautions should be practiced to avoid inoculation of any body fluids on mucosa or into skin. Those who see patients at some frequency could get pre-exposure immunization.

The only instances of well documented human-to-human rabies virus transmission have been due to corneal transplantation. The donors had died of ascending paralysis, which is one form of human rabies. The diagnosis of rabies was missed, corneae transplanted

and the recipients subsequently developed rabies and died.

Q 5. *Do cats transmit rabies?*

A 5. Yes, cats are the second commonest species that transmit rabies virus infection in our country. Since cats seldom bite, cat bites are more often the result of rabies than are dog bites. However, cats with kitten may be aggressive and bite while defending the kitten. In all cases of cat bites the circumstances should be examined in depth. Washing of the wound as well as the dosage of rabies vaccine are to be followed just as in the case of dog bites.

Q 6. *Among the 3 cell culture rabies vaccines, which is the best?*

A 6. As the question implies, there are 3 different rabies vaccines of cell culture origin available in India. They are the human diploid cell vaccine (HDCV), the purified chick embryo cell vaccine (PCEC) and the Vero cell vaccine. Although the cell culture substrates are different, the final product is a suspension of purified and inactivated rabies virus, with potency adjusted to meet internationally accepted standards. Contaminating proteins or nucleic acids from the cell substrates are so low in quantity that they are undetectable by ordinary laboratory tests. Hence, if a vaccine is given to a laboratory, it will be well nigh impossible to identify the cells of origin of the killed virus. Thus, these 3 vaccines are nearly identical in terms of antigenic content and quality. The purity of the product is the reason for its safety from untoward adverse reactions.

The PCEC is now manufactured in India by a multinational company. A manufacturing facility for Vero cell vaccine

was built in India, but the Government decided to close it even before production started. The Pasteur Institute (Coonoor) has successfully made test batches of Vero cell rabies vaccine and large scale production is possible soon.

Q 7. *Intradermal immunization requires only a fraction of the intramuscular dose. Can this method be adopted for post-exposure prophylaxis in order to reduce costs?*

A 7. It is true that fractional doses given intradermally are almost as effective as full doses given intramuscularly. In fact several studies have been conducted to ascertain if intradermal (ID) immunization with rabies vaccine would induce satisfactory immunity to protect against rabies. Different dosage schedules have been suggested for this purpose. In the hands of experts ID immunization has been successful.

However, this method cannot be recommended for general use. The exact ID placement of vaccine is not guaranteed when inexperienced persons inject. The volume of vaccine is either 0.1 or 0.2 ml; some leakage or loss in the dead space of needle and syringe may reduce the actual volume injected. If treatment failure occurs, the physician could be accused of 'non-standard' practice. For these reasons ID immunization cannot be recommended for general use. In specific centers where expertise for antibody measurement is available, ID route could be practiced with antibody tests in representative samples. For ID immunization to be practiced, there should be sufficient numbers of dog-bite victims available for utilizing the entire vaccine in the vial so that vaccine is not wasted.