

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 answers 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

Q1. When very cheap sheep-brain anti-rabies vaccine is available in India, why should the more expensive and imported cell-culture rabies vaccines be used?

A1. Although it is true that the sheep-brain rabies vaccine is very cheap to produce, it is not a safe vaccine for human use. Many countries in which sheep-brain vaccine was being used prior to the widespread availability of the newer cell culture vaccines, have banned its use. It is true that historically animal-brain rabies vaccines have had a great role in rabies prevention. Between the risk of rabies and the risk of adverse reaction to the animal-brain vaccine, the latter was the lesser of the two evils. However, it could never be given when there was no real risk of rabies nor could it be used for pre-exposure prophylaxis since it was not safe enough for these purposes.

Approximately 1 in 3000-5000 persons given animal-brain rabies vaccine develops a neurological illness affecting the spinal cord, nerve roots, peripheral nerves or brain, often in combination. Occasionally, respiratory paralysis or meningoencephalitis might cause death in the vaccinated person. Recovery from limb paralysis may take several months; bladder paralysis may last even longer. The pathogenesis of this adverse reaction, called "neuromyolytic accident", is immune demyelination due to the myelin protein content in the vaccine.

With the advent of the safe cell culture rabies vaccines some 2 decades ago, the animal-brain rabies vaccine has become obsolete. In my personal opinion it is unethical to use animal brain rabies vaccine in human beings. It is nothing but a matter of national shame that we continue to manufacture, distribute and use sheep-brain rabies vaccine even in 1995.

Q2. Rabies vaccine is usually given to treat dog-bites. Is it a therapeutic agent or a vaccine? If it is a vaccine, why is it not recommended for routine use like other vaccines?

A2. A product that induces immunity in order to protect against a disease is called vaccine. Even though rabies vaccine is usually given after dog-bites, the purpose is not to 'treat' the bite, but to prevent rabies. Animal bite is a mode of rabies virus transmission. Even if rabies virus is inoculated by the animal bite, since the incubation period is long, there is usually sufficient time to protect the person by active immunization (when the incubation period is likely to be short, then passive immunization can offer early protection). Thus, rabies vaccine is usually used for 'post-exposure prophylaxis'. Earlier, we have discussed the use of hepatitis B vaccine for post-exposure prophylaxis. Rabies vaccine can certainly be used for pre-exposure immunization also.

However, the incidence of animal bites requiring rabies prophylaxis is very low in the community. Routine immunization of all children for rabies vaccine is, therefore, not recommended. Moreover, the cost of the vaccines available on the market is too high to be afforded by either the Government or by all families for routine use. On the other hand, people at risk of rabies exposure, such as veterinarians, laboratory workers, animal handlers, *etc.* should be immunized to protect against the occupational hazard of rabies exposure. If cost is of no concern, in motivated families, especially those who own pets or love animals, or do frequent outdoor activities, pre-exposure rabies immunization is a good idea. The vaccine is completely safe for this purpose. It can be given at any age, from infancy upwards.

Q3. *What is the dosage schedule of post-exposure rabies vaccination?*

A3. The vaccine dose is the same for all age groups. The course consists of 5 doses given on days 0, 3, 7, 14 and 30. Day 0 is the day of dog-bite. If for some reason the first dose is given after some delay, then the intervals can be re-adjusted as shown in the following examples. If the first dose is given on day 1 or 2, further doses are on days 3, 7, 14 and 30. If the first dose is given on day 3, the next doses are given on 4, 7, 14 and 30.

Q4. *What is the dosage schedule of passive post-exposure rabies immunization?*

A4. The antibody content of antirabies serum (ARS) or human rabies immune globulin (HRIG) is quantified as international units (IU). For ARS the dose to be given is 40 IU/kg and for HRIG

it is 20 IU/kg body weight. Half the volume is to be given around the site of bite and the other half is to be given intramuscularly. The ARS is usually raised in horses. Before it is injected, a skin test should be done. If immediate hypersensitivity reaction occurs then instead of ARS, HRIG should be given. If HRIG is not available then desensitization should be done using ARS according to standard methods.

When passive immunization is given, the active immunization consists of 6 doses of vaccine, given on days 0, 3, 7, 14, 30 and 90.

Q5. *Should rabies vaccine be given after all dog-bites?*

A5. No, it is not necessary to give rabies vaccine after all dog bites. When there is no risk of rabies virus transmission, there is no need to give rabies immunization. Therefore, each incident of dog bite must be individually evaluated in detail. Sometimes a bite may not have broken the skin at all. In that case, there is no risk of rabies virus inoculation. When in doubt the bite site should be examined with a hand-lens. The bite of a well immunized dog also poses no risk of rabies. However, the fact that the biting dog was properly immunized against rabies should be verified and not simply accepted on hearsay evidence. Similarly, a previously immunized subject may not need vaccination, or may need only one or two booster doses, depending on the circumstances of dog bite.

When a healthy but unprotected dog bites in response to clear provocation, the decision to give rabies vaccine or not, and the design of the course of vaccination, depend upon several factors. Such factors include the site of bite, the availability of the dog for daily observation and the presence or absence of animal rabies in the locality and season.

Persons with dog-bite should be counseled regarding the risks and benefits of

vaccination. It is also ideal that the persons (or parents in case of children) also participate in the decision-making process.

Q6. *Can healthy dogs transmit rabies virus?*

A6. Dogs infected with rabies virus remain healthy during the incubation period. Then the virus infection progresses and the salivary glands are infected. At this time the saliva contains virus; yet the animal shows little or no signs of abnormal behavior or illness. Within a few days the brain of the dog is infected and now the animal develops the symptoms and signs of rabies. These include excessive salivation, not eating food, abnormal behavior, irritability and biting of objects, other animals or humans, and not responding to the owners. Some animals become unusually quiet and lethargic. Some get paralysed. The biting variety is called 'furious' rabies and the paralytic variety called 'dumb' rabies. In summary, the saliva of the dog may contain rabies virus 2-3 days prior to the animal showing other recognizable abnormalities. During these 2-3 days the dog does not usually bite; however, if an animal is provoked it may bite. Thus, a healthy-looking animal may transmit rabies virus. However, that animal will develop sickness and will die within a maximum period of 7 or 8 days. This is the reason for the rule of thumb namely, that if a dog is alive for 10 days after biting, there has been no risk of rabies virus infection.

There is another issue which should also be addressed here. There have been very rare instances of a carrier state of rabies virus in dogs. This phenomenon was first described by Dr. Veeraraghavan, in Pasteur Institute, Coonoor. Since then this occurrence has been confirmed elsewhere; however, it is indeed a rare phenomenon. Therefore, the very remote possibility of the dog in question in a specific instance being a carrier is not to be taken as a reason to give rabies

vaccination to every victim of dog-bite.

Q7. *Do dogs vaccinated against rabies transmit rabies?*

A7. Dogs fully vaccinated against rabies are themselves protected against rabies as well as rabies virus multiplication within their salivary glands. Therefore, even if they are bitten by rabid dogs they do not get infected; hence they cannot transmit rabies virus. However, one must be aware of spurious rabies vaccines in the market; moreover, occasionally expired vaccine may be used. For these reasons details about the vaccination of the dog must be checked before accepting that a dog was satisfactorily vaccinated. Unless convinced about the vaccination status of the biting dog, one must be cautious in making decisions on that basis.

Q8. *Can rabies virus be transmitted through licks or scratches?*

A8. The answer is yes; if rabies virus is present in the saliva, the lick on a mucosal surface (mouth, eyes, vagina) carries some risk of virus inoculation. However, licks on intact skin cannot transmit rabies virus. On fresh cut or wound, and on open ulcer there exists the probability of virus entry. Similarly scratches by rapid animals resulting in the break of skin also carry the risk of virus transmission since the paws may be wet with saliva. In rabid animals there is usually excessive salivation.

Q9. *The rabies virus is inoculated presumably when the dog bites. In that case, how does immunization protect after a dogbite, when rabies virus is already inoculated?*

A9. There are some critical steps in the development of rabies following exposure. The first critical step of course is the inoculation of rabies virus into the wound or the mucosa. For infection to progress, the virus has to enter a susceptible cell, such as a

fibroblastic cell or a muscle cell. Such entry begins with virus attachment to the cell membrane followed by its entry into the cell. This is the second critical step. After local virus multiplication for several generations through the infection of new host cells, the virus gains access to a nerve ending. This is the third critical step. Thereafter the virus travels via the nerve pathway to the epinal cord and then spreads within the central nervous system to reach the brain. This is the final critical step.

Soon after a dog bites, while virus has been deposited, but not yet has become intracellular, thorough washing with water and soap often results in the removal of the virus particles from the wound. This is the most important procedure in preventing rabies virus infection after a dog-bite. Soap actually dissolves the lipid envelope of the virus rendering it non-infectious. Soap also removes virus particles by detergent action.

It is generally believed that immunity by way of the presence of virus neutralizing antibodies prevents the attachment of virus particles to the nerve endings (the third critical step). It is also generally believed that this critical step usually occurs a few to several days after the first critical step (the dog bite).

In some cases this interval may be weeks

or even months. It is this time interval before the third critical event that allows immunization to become protective even after the bite of the dog. For this reason, the earlier antibody production can be induced, the better. Therefore doses of vaccine are given on days 0,3 and 7; many individuals develop measurable antibody levels on day 7 or 10, and all persons develop detectable antibody by day 14. The doses on days 14 and 30 are to sustain high antibody levels for prolonged periods. When the dog bite is in an area where nerve endings are more widely distributed, such as face, scalp, neck, palms of hand or genitalia, it is important to provide antibody protection as soon as possible; for this reason passive immunization is a must in such cases.

We are not sure if immunity can protect if induced after virus enters the nerve path-. way. Obviously the farther the site of bite from the brain, the longer it takes the virus to travel. This may be one reason for longer incubation periods with lower limb bites than with bites on head or neck. However, when the bite is by a presumably rabid dog, passive immunization is to be given irrespective of the site of bite. By injecting part of the ARS or HRIG around the site of bite, we ensure high antibody levels in the tissue fluids at the site of bite. This prevents the multiplication of rabies virus in fresh host cells, and it also prevents the entry of virus into nerve endings.

