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WHO Recommendations on Rabies Post-Exposure Treatment and the Correct Technique of Intradermal immunization against Rabies

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GUIDE FOR RABIES POST-EXPOSURE TREATMENT

THE DECISION TO TREAT

The circumstances of the bite or other contact and the behaviour and appearance of an animal may suggest that it is rabid.¹ An attack by an unusually excitable or partially paralysed mammal, which is a known rabies vector in that area, indicates a high risk of exposure to rabies. However in rabies endemic areas, the risk of infection should be considered if there is any exposure to a known rabies vector species.

Although unvaccinated animals are more likely to transmit rabies, vaccinated animals can also do so if the vaccination was ineffective for any reason. The risk of a dog being infected with rabies is greatly reduced when it appears healthy and there is a firm history of vaccination with a minimum of 2 immunizations with a potent rabies vaccine. Under these circumstances, a biting dog may be observed for 10 days and the bitten patient need not have treatment. If the dog shows any sign of illness, during the observation period, the patient should receive urgent full post-exposure therapy.²

The recommendations given here are intended as a general guide. In certain situations, these procedures may be modified. Such situations include exposure of infants or those unable to give a reliable history.

These patients may be treated as category II or III (see table, page 3). Combined immunoglobulin-vaccine treatment is considered as the best specific systemic treatment available for the post-exposure prophylaxis of rabies in humans, although experience indicates that vaccine alone is sufficient for minor exposures (category II).

Treatment may be discontinued if the animal involved (dog or cat) remains healthy throughout an observation period of 10 days; or if the animal is euthanised and found to be negative for rabies by laboratory tests. If a biting animal is suspected of being rabid, immediate euthanasia and appropriate laboratory examination should be performed.

Treatment should be started as early as possible after exposure, but it should not be withheld from exposed persons whatever time interval has elapsed.

LOCAL TREATMENT OF WOUNDS INVOLVING POSSIBLE EXPOSURE TO RABIES -RECOMMENDED IN ALL CASES

1. First-aid treatment

Since elimination of rabies virus at the site of infection by chemical or physical means is the most effective mechanism of protection, immediate vigorous washing and flushing with soap and water, detergent or water alone are imperative (this procedure is recommended for all bite wounds, including those unrelated to possible exposure to rabies). Then apply either ethanol (700 ml/l) or tincture or aqueous solution of iodine or povidone iodine.

2. Treatment by, or under direction of, a physician

Treat as described above and then:

- apply anti-rabies immunoglobulin by careful instillation into the depth of the wound and by infiltration around the wound;
- postpone suturing of the wound; if suturing is necessary, ensure that immunoglobulin has been applied locally as described above;
- where indicated, begin anti-tetanus treatment and administer antimicrobials and drugs to control infections other than rabies.

EMERGING AND OTHER COMMUNICABLE DISEASES SURVEILLANCE AND CONTROL

Guide for post-exposure treatment

Category	Type of contact with a suspect or confirmed rabid domestic or wild ^{a)} animal, or animal unavailable for observation	Recommended treatment
I	Touching or feeding of animals Licks on intact skin	None, if reliable case history is available.
II	Nibbling of uncovered skin Minor scratches or abrasions without bleeding Licks on broken skin	Administer vaccine immediately ^{b)} . Stop treatment if animal remains healthy throughout an observation period ^{c)} of 10 days or if animal is euthanised and found to be negative for rabies by appropriate laboratory techniques.
111	Single or multiple transdermal bites or scratches Contamination of mucous membrane with saliva (i.e. licks)	Administer rabies immunoglobulin and vaccine immediately. ^{b)} Stop treatment if animal remains healthy throughout an observation period ^{c)} of 10 days or if animal is killed humanely and found to be negative for rabies by appropriate laboratory techniques.

- ^a Exposure to rodents, rabbits and hares seldom, if ever, requires specific anti-rabies treatment.
- ^b If an apparently healthy dog or cat in or from a low-risk area is placed under observation, it may be justified to delay specific treatment.
- ^c This observation period applies only to dogs and cats. Except in the case of threatened or endangered species, other domestic and wild animals suspected as rabid should be euthanised and their tissues examined using appropriate laboratory techniques.

CELL CULTUREAND **P**URI**F**IED DUC**K**EMBR**Y**O VACCINES

The volume of vaccine per dose, the number of doses recommended in a given situation and the route of administration may vary.

The use of modern, inactivated, purified cell-culture and purified duck embryo vaccines should, where economically and technically feasible, replace those produced on brain tissue in both developed and developing countries.

These vaccines with a potency at least 2.5 IU per single intramuscular (im) dose should be applied according to one of the following schedules. (See also diagram)

Intramuscular schedules:

One dose of the vaccine should be administered on days 0, 3, 7, 14 and 28. All im injections must be given into the deltoid region or, in small children, into the anterolateral area of the thigh muscle. Vaccine should never be injected into the gluteal region.

As an alternative, the 2-1-1 regimen may be used. Two doses are given on day 0. One dose is given in the deltoid region of the right arm and a second dose at the same site in the left arm. In addition one dose is given in the deltoid region on day 7 and one on day 21.

Intradermal schedules:

Two intradermal (id) regimens have been demonstrated to be immunogenic. (See Part 2, Guidelines for the correct technique of intradermal immunization against rabies.)

a) 2-site intradermal method ("2-2-2-0-1-1")

For use with purified vero cell vaccine (PVRV), purified primary chick embryo cell vaccine (PCECV) and purified duck embryo vaccine (PDEV). The volume of an im dose after reconstitution is 0.5 ml for PVRV, 1 ml for PCECV and currently also 1ml for PDEV. PDEV should become available in 0.5 ml (volume after reconstitution) in 1998.

Standard WHO intramuscular regimen Dose: one im dose (1.0 or 0.5 ml) into deltoid Day 0 3 14 28 5 vials 5 visits ŧ Rabies immune globulin Reduced multisite intramuscular regimen (2-1-1) Dose: one im dose (1.0 or 0.5 ml) into deltoid Day 0 Sites x2 7 21 x1 x1 4 vials 3 visits 4 Rabies immune globulin 8-site intradermal regimen (8-0-4-0-1-1) Dose: 0.1 ml id per site Day 0 Sites x8 90 x1 7 28 x4 x1 <2 vials 4 visits 1 Rabies immune globulin 2-site intradermal regimen (2-2-2-0-1-1) Dose: one id dose = one fifth of im dose (0.1 or 0.2 ml), id per site Day 0 Sites x2 90 x1 28 3 7 x2 x2 x1 <2 vials 5 visits ŧ Rabies immune globulin

The volume of the id dose is one fifth of the im dose per site. It varies according to the volume of the im dose: i.e. if im dose is 0.5 ml, id dose = 0.1 ml/site, if im dose is 1.0 ml, id dose = 0.2 ml/site (but if this is not technically possible, divide between two sites close together).

Regimen:

Days 0, 3 and 7:	1 id dose $(0.1 \text{ ml or } 0.2 \text{ ml according to vaccine type})$ is given at each of 2 sites, intradermally on upper arm, over each deltoid
Days 28 and 90:	1 id dose (0.1 ml or 0.2 ml according to vaccine type) is given at one site, on upper arm

b) 8-site intradermal method ("8-0-4-0-1-1")

For use with human diploid cell vaccine (HDCV) and purified chick embryo cell vaccine (PCECV) where the im dose is 1 ml after reconstitution.

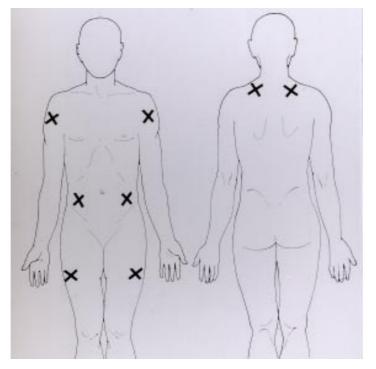
Regimen:

Day 0:	0.1 ml of reconstituted vaccine is given at each of 8 sites using the contents of a whole vial. Inject intradermally over deltoid, lateral thigh, suprascapular region and lower quadrant of the abdomen (see diagram page 7)
Day 7:	0.1 ml of vaccine is given at each of 4 sites over deltoids and thighs

Days 28 and 90: 0.1 ml of vaccine is given at one site, over deltoid

These id regimens require considerably less vaccine than the im regimens. Using aseptic technique, a dose of vaccine may be withdrawn from a vial and the remainder used for another patient, provided that the vial is stored in a refrigerator at 4 to 8° C. A sterile needle and syringe must be used to draw up vaccine for each patient. Reconstituted vaccines should be used as soon as possible and those without preservative should be used within 6 to 8 hours if kept at 4 to 8° C.

INJECTION SITES



Distribution of injection sites used on day 0 of the 8-site intradermal regimen

PART

NERVOUS TISSUE VACCINES

If modern rabies vaccine is not yet available, brain tissue vaccine (preferably suckling mouse brain - SMB - vaccine) should be administered. SMB vaccines should have a potency of at least 1.3 IU per dose regardless of the number of doses required for full postexposure treatment. Reduced subcutaneous schedules with SMB vaccines are used particularly in Latin American countries. They generally consist of 7 daily subcutaneous doses and boosters given at 10, 20 and 90 days after the first injection. For other nervous tissue vaccines, prepared in sheep or goat brain tissue, national authorities should recommend a schedule of immunization that has been shown to be protective. None of these nervous tissue vaccines has been shown to be protective or immunogenic applied by the id route.

USE OF RABIES IMMUNE GLOBULIN (RIG)

Rabies immune globulin (RIG) should be given in a single dose of 20 IU per kg of body weight for human RIG, and 40 IU per kg of body weight for heterologous (equine) RIG; at the same time as the first dose of vaccine.

The RIG should be infiltrated around and into the wound, even if the lesion has begun to heal. Care is needed when injecting into tissue compartments, for example into a finger. Any remaining RIG should be injected im at a site distant from the site of vaccine inoculation.

If RIG is unobtainable when the first dose of vaccine is given, it may be given up to day 7.

The total recommended dose of RIG must not be exceeded as it may reduce the efficacy of the vaccine. If the calculated dose of RIG is insufficient to infiltrate all wounds, sterile saline can be used to dilute it 2 or 3 fold to permit thorough infiltration.³

Serum sickness occurs in 1% to 6% of patients usually 7 to 10 days after injection of equine RIG, but it has not been reported after treatment with human RIG.

Skin testing for hypersensitivity to equine RIG

Skin testing may detect the rare case of IgE mediated (Type I) hypersensitivity to equine serum protein. However, the majority of reactions to equine RIG result from complement activation, are not IgE mediated, and will not be predicted by skin testing.⁴

A negative skin test must never reassure the physician that no anaphylactic reaction will occur. Those administering equine RIG should always be ready to treat early anaphylactic reactions with adrenaline/epinephrine. The dose is 0.5 ml of 0.1 per cent solution (1 in 1000, 1 mg/ml) for adults, and 0.01 ml/kg body weight for children, injected subcutaneously or im.

If the skin test is positive, treatment with equine RIG or preferably human RIG should proceed if indicated, but special precautions should be taken if equine RIG are used (e.g. pretreatment with adrenaline/epinephrine im and with antihistamine) and the patient observed for at least one hour after the injection.

Techniques of skin testing have not been standardised. National guidelines should be followed.

POST-EXPOSURE TREATMENT OF PREVIOUSLY VACCINATED PATIENTS

Patients exposed to rabies who have previously received cell culture or purified duck embryo rabies vaccine have the advantage that booster doses of vaccine will rapidly induce a large increase in antibody production (a "secondary response"), but this treatment is still needed urgently.

A short course of a cell culture or purified duck embryo vaccine can be given providing that the patient has previously had a complete pre- or post-exposure course of one of these vaccines, or that rabies neutralizing antibody (>0.5 IU/ml) has been demonstrated at some time in the past. No RIG treatment is necessary.

- Regimen: One injection of vaccine is given on days 0 and 3. The dose is either one standard im dose, which may be 1 ml or 0.5 ml according to vaccine type, or one intradermal dose.
- Caution: If antimalarial chemoprophylaxis (e.g. with chloroquine) is being given concurrently, im injections are mandatory.

If an id injection does not raise a satisfactory papule (see "procedure"), a second id injection should be given in the opposite arm.

PRE-EXPOSURE VACCINATION

This is recommended for anyone at increased risk of exposure to rabies virus, including laboratory staff working with rabies, veterinarians, animal handlers, zoologists, wildlife officers and other people living in or travelling to rabies endemic areas where dogs are the dominant rabies vector species.

Pre-exposure vaccine regimen:

Three doses of a cell culture or purified duck embryo vaccine are given on days 0, 7 and 21 or 28. A few days' variation in timing is acceptable. The dose is either 1 standard im dose, which may be 1 ml or 0.5 ml according to vaccine type, or 0.1 ml id for all vaccine types. This id regimen has not been tested with PDEV.

If antimalarial chemoprophylaxis (e.g. with chloroquine) is being used concurrently, im injections are preferable, as the antibody response may be impaired if the id method is used.

Because of the possible hypersensitivity, as seen with HDCV, repeated booster injections should be given only when necessary to people at high or continuing risk of infection. Laboratory staff and others at high/ continuing risk of exposure should have their neutralizing antibody titre checked every six months. If it is less than 0.5 IU/ml a booster dose of vaccine should be given.

EMERGING AND OTHER COMMUNICABLE DISEASES SURVEILLANCE AND CONTROL

INJECTION EQUIPMENT



One ml syringe and needle for intradermal injection

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EMERGING AND OTHER COMMUNICABLE DISEASES SURVEILLANCE AND CONTROL

CORRECT PROCEDURE FOR INTRADERMAL VACCINE INJECTION

Inserting needle intradermally



Injecting vaccine intradermally against resistance





Final blanched papule



Appearance on day 7 of 2-site id vaccine course, showing two previous injection sites

GUIDELINES FOR THE CORRECT TECHNIQUE OF INTRADERMAL IMMUNIZATION AGAINST RABIES

Introduction

The continuing problem of rabies is most severe in developing countries of Africa, Asia and South America, where more than 99% of all the world's human rabies deaths occur. Rabies vaccine of any kind is often in short supply in these areas and patients may not complete post-exposure vaccination courses. Rabies immune globulin (RIG) is usually unobtainable; it was given to only 1% of patients receiving post-exposure treatment in 1993 in Asia and Africa.⁵

Post-exposure treatment

The treatment is needed after possible contact with rabies virus through an open wound or mucous membrane. Intact skin is a barrier against infection. The risk of rabies must be assessed for each individual patient (see first section on "decision to treat").

Post-exposure treatment consists of three important elements:

- 1. Wound cleaning (see page 2).
- 2. Active immunization with vaccine
- 3. Passive immunization with rabies immune globulin (see pages 8 and 9)

CHOICE OF RABIES VACCINESAND ECONOMICAL REGIMENS

Rabies vaccines of nervous tissue origin, e.g. Semple, Fermi or suckling mouse brain vaccines, are still widely used, but these are outdated and should be replaced by safer cell culture vaccines and purified duck embryo vaccines. The standard im vaccine regimen may be used but if insufficient vaccine is available, alternative more economical regimens using less vaccine injected id can produce a comparable degree of protection against rabies.

The following vaccines, meeting WHO requirements, have been tested for id post-exposure treatment in limited trials.⁶⁻¹¹

Human diploid cell vaccine (HDCV) Rabivac™

Purified vero cell vaccine (PVRV) Verorab[™], Imovax - Rabies vero[™] TRC Verorab[™]

Purified chicken embryo cell vaccine (PCECV) Rabipur™

Purified duck embryo vaccine (PDEV) Lyssavac NTM

Other vaccines for human use have been given effectively by intradermal injection at a single site, e.g. typhoid, cholera and BCG.

A number of precautions should be adhered to when the id technique is used, including staff training, conditions and duration of vaccine storage after reconstitution, and use of appropriate 1 ml syringes and short hypodermic needles.

The decision to implement economical id post-exposure treatment rests with government agencies which select policies for rabies prophylaxis in their own countries.

INTRADERMAL (ID) REGIMENS (see page 5)

Two intradermal regimens have been demonstrated to be immunogenic: (See Annex 1 for details of studies)

a) 2-site intradermal method ("2-2-2-0-1-1")

For use with purified vero cell vaccine (PVRV), purified primary chick embryo cell vaccine (PCECV) and purified duck embryo vaccine (PDEV). The volume of an im dose after reconstitution is 0.5 ml for PVRV, 1 ml for PCECV and currently also 1 ml for PDEV. PDEV should become available in 0.5 ml (volume after reconstitution) in 1998. The volume of the id dose is one fifth of the im dose per site. It varies according to the volume of the im dose: i.e. if im dose is 0.5 ml, id dose = 0.1 ml/site, if im dose is 1.0 ml, id dose = 0.2 ml/site (but if this is not technically possible, divide between two sites close together).

Regimen:

Days 0, 3 and 7:	1 id dose (0.1 ml or 0.2 ml according to vaccine type) is given at each of 2 sites, intradermally on upper arm, over each deltoid	
Days 28 and 90:	1 id dose (0.1 ml or 0.2 ml according to vaccine type) is given at one site, on upper arm	
b) 8-site intradermal method ("8-0-4-0-1-1")		
For use with human diploid cell vaccine (HDCV) and purified chick embryo cell vaccine (PCECV) where the im dose is 1 ml after reconstitution.		
Regimen:		
Day 0:	0.1 ml of reconstituted vaccine is given at each of 8 sites using the contents of a whole vial. Inject intradermally over deltoid, lateral thigh, suprascapular region and lower quadrant of the abdomen (see diagram page 7)	

Day 7: 0.1 ml of vaccine is given at each of 4 sites over deltoids and thighs

Days 28 and 90: 0.1 ml of vaccine is given at one site, over deltoid

WHEN SHOULD ID IMMUNIZATION BE USED?

People of all ages may be given vaccine id, including pregnant women.¹²

The method is particularly appropriate where vaccine or money are in short supply, and in centres dealing with numbers of bitten patients, where there is an established cold chain and well-trained staff. The 8-site id regimen should be considered when no RIG is available.

CORRECT TECHNIQUE OF ID IMMUNIZATION

Equipment required:

A vial of a recommended rabies vaccine and diluent.

A sterile 1 ml syringe, graduated with markings at least every 0.05 ml (either a Mantoux syringe or preferably an insulin syringe with a fixed needle).

A sterile 25 or 27 gauge short hypodermic needle (13 mm or less).

Disinfectant swabs (e.g. 70% ethanol, isopropyl alcohol) for cleaning the top of the vial and the patient's skin.

Procedure

Reconstitute the vial of freeze-dried vaccine with diluent supplied by the manufacturer, using aseptic technique. With the 1 ml syringe, draw up the volume of vaccine needed to treat one patient, allowing for any dead space in the syringe. Expel any air bubbles carefully. Using the technique for BCG inoculations, stretch the surface of the skin and insert the tip of the needle, bevel upwards, almost parallel to the skin surface and slowly inject the vaccine into the uppermost layer of skin. If the needle is correctly placed, considerable resistance is felt. A raised papule should begin to appear immediately causing a "peau d'orange" (orange peel) appearance. Some difficulty may arise with elderly patients who have thin, inelastic skin, and with squirming infants. Those inexperienced with the technique should practice using 0.1 ml of isotonic saline until they can reliably produce a peau d'orange papule.

If the vaccine is injected too deeply into the skin, and a papule is not seen, the needle should be withdrawn and reinserted nearby. If there is complete failure to inject intradermally at more than half of the multiple injection sites, a single extra intradermal dose should be given.

Record treatment

Hospital records should include the vaccine type, batch number and treatment regimen. The timing of future injections must be emphasised by means of an appointment card given to each patient.

Storage of reconstituted vaccines

If great care is taken with aseptic technique, an appropriate dose of vaccine may be withdrawn from a vial and the remainder used for another patient, provided that the vial is kept cool and is stored in a refrigerator at 4 to 8° C. A sterile needle and syringe must be used to draw up vaccine for each patient, to prevent cross-infection of hepatitis, HIV and other infections.

Although the vaccine antigen is very stable at 4°C, there is a high risk of contamination of multidose vials by microorganisms, especially if the vaccine does not contain a preservative. Reconstituted vaccines should be used as soon as possible and those without preservative should be used within 6 to 8 hours if kept at 4 to 8°C.

SIDE EFFECTS OF ID VACCINE TREATMENT

Throughout 20 years of use, tissue culture vaccines have proved remarkably safe and free of significant complications.

Mild symptoms of pain, erythema, irritation or swelling at the intradermal injection sites occur in 13% to 92% of patients.^{7,13} The most frequent symptom is local irritation in 7% to 64% of vaccinees.^{7,13} Generalized symptoms reported by 3% to 14% of recipients include headache, fever and influenza-like illness.^{7,8} Transient maculopapular and urticarial rashes are occasionally seen.

DATA SUPPORTING THE RECOMMENDED ID POST-EXPOSURE REGIMENS

a) 2-site intradermal method ("2-2-2-0-1-1")

Following a serological study in volunteers, ¹⁴ the 2-site id regimen with PVRV was tested in 100 patients with proven exposure to rabid animals.⁸ All patients also received RIG and were followed up for 1 year. No deaths from rabies occurred, and rabies neutralizing antibody in the 10 patients' sera tested were all >0.5 IU/ml after 1 year. This regimen has been given, with PVRV, to more than 70,000 patients in Thailand, where it has been in routine use for several years, and to more than 12,000 patients in the Philippines. Studies with PCECV id have been reported, ^{9,10} and using a 1 ml vial of PDEV, an id dose of 0.2 ml also gave satisfactory serological results.¹¹

b) 8-site intradermal method ("8-0-4-0-1-1")

This regimen was derived from two serological studies in volunteers.^{15,16} It was then tested in a post-exposure study of patients bitten by proven rabid animals.⁶ Out of a total of 155 patients, 78 received the 8-site id HDCV, and 36 of these, with severe exposure, also had RIG. Rabies neutralizing antibody levels were monitored frequently. No deaths from rabies occurred during 2 years follow-up. By day 7, antibody was detected in 88% of 42 patients who did not have RIG, and at 1 year all 72 patients tested had antibody, in 69 (96%) the level was >0.5 IU/ml. This method has a wide margin of safety since an adequate antibody response is produced if only 4 of the 8 injections are intradermal.¹⁶ The 8-site regimen gave similar serological responses when used with PCECV.⁷

Vaccine potency

Vaccine should contain at least 2.5 IU per im dose. Cell culture and purified duck embryo vaccines used with the 2-site id post-exposure regimen therefore have a potency of at least 0.5 IU/id dose, whether it be 0.1 or 0.2 ml.



LIST OFABBREVIATIONS

day 0	the day on which the first dose of a vaccine course is
	given
id	intradermal
im	intramuscular
IU	International Unit
HDCV	human diploid cell vaccine
PCECV	purified chick embryo cell vaccine
PDEV	purified duck embryo vaccine
PVRV	purified vero cell vaccine
RIG	rabies immune globulin
2-2-2-0-1-1	description of the 2-site id regimen: the number of sites of id injection given on the days of the original Essen im regimen:
	day 0, 3, 7, 14, 28 & 90
8-0-4-0-1-1	description of the 8-site id regimen, as above.

REFERENCES FOR FURTHER INFORMATION

Information on all aspects of rabies:

WHO Expert Committee on Rabies. Eighth Report. Technical Report Series 824. Geneva: World Health Organization, 1992.

Information on:

How to take an animal brain biopsy Techniques for laboratory diagnosis Rabies-related viruses Lists of rabies virus reference laboratories

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