Continuing Dilemma in Endemic Infection: Rabies in Focus

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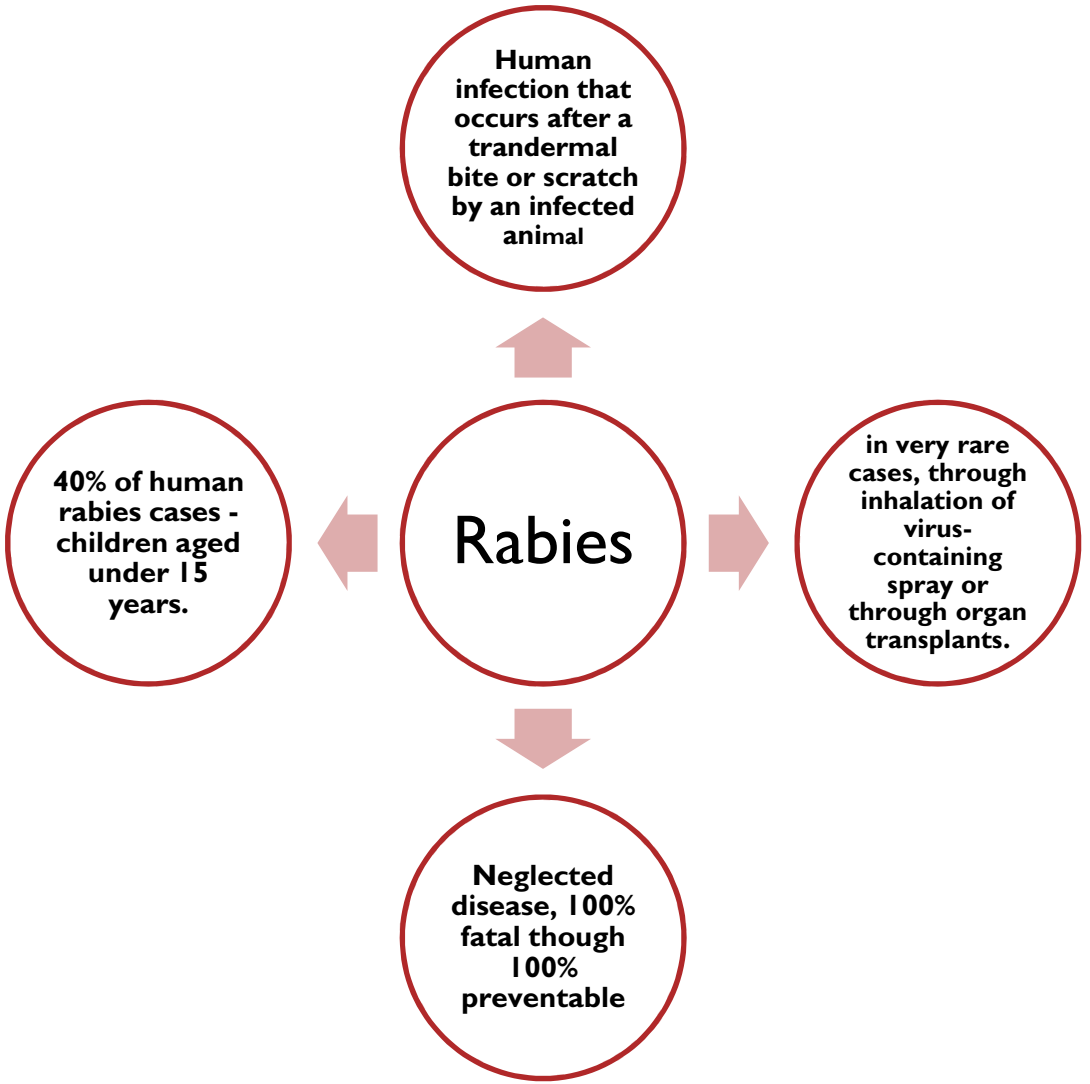
Conflict of Interest Disclosure

Currently an employee of GSK Phils

Objective

- To provide update to rabies status in the Philippines
- To address Frequently Asked Questions in Rabies Management

Rabies Facts



Rabies Status: Philippines

- In 2015, a total of 432,458 animal bite cases were recorded by DOH
- 226 reported deaths due to rabies.

480 Animal Bite Treatment Centers (ABTCs) nationwide

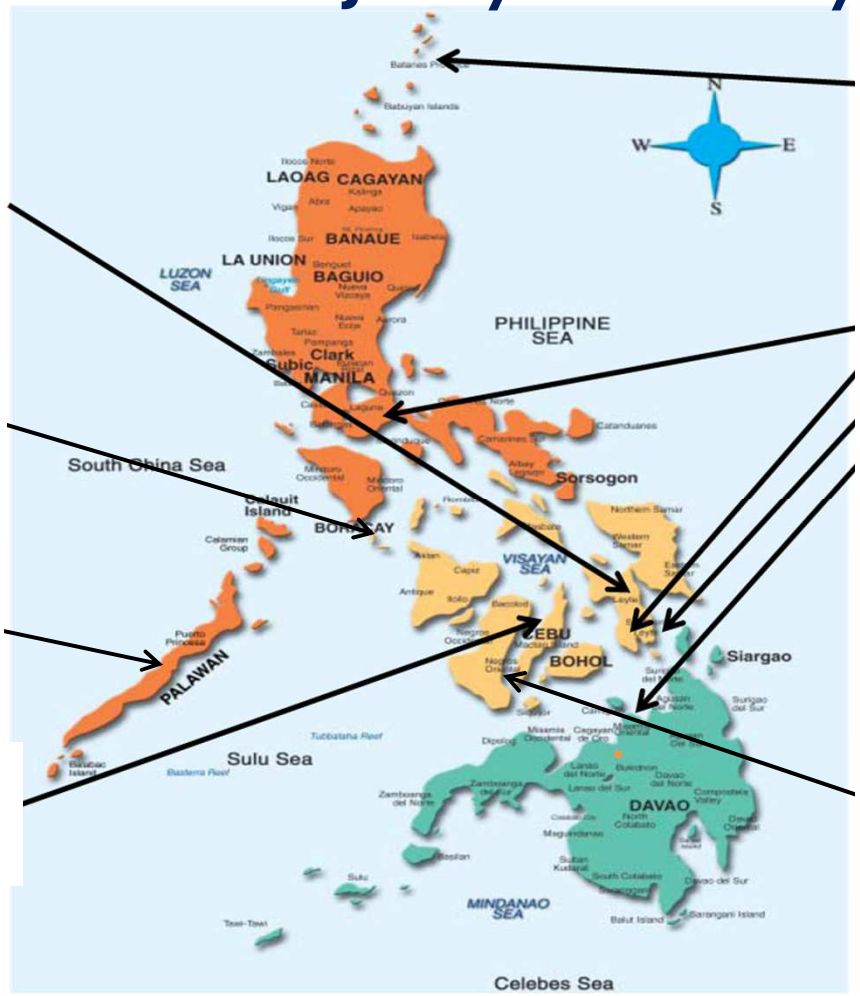
DOH, Jan 4, 2016 Press Release

DOH WILL PROVIDE FREE ANTI-RABIES VACCINES THIS YEAR PRESS RELEASE/JANUARY 4, 2016

As part of the rabies elimination campaign, a total of 33 provinces/areas were declared 'rabies-free' by DOH and Department of Agriculture, Bureau of Animal Industry (DA-BAI).

Disease Free Zone Initiative

Rabies Free Areas Jointly Declared by DOH and DA



RABIES FREE ZONES (as of Feb 2016)

- Siquijor
- Batanes,
- Apo Island in Negros Oriental,
- Camotes islands
- Malapascua
- Biliran
- Camig
- Marinduqu
- Limasawa
- C
- Boracay
- Dinagat
  - Sa
  - Dinagat
  - Loreto
  - Cagdiano
  - Libjo
  - Basilisa(Rizal and Tubajon)
- C ron
- lion
- suanga
- aba
- ed
- gsaysay
- Cagayancillo
- Tingloy
- Agutaya
- Balabac

Rabies Free Phils in 2020

Rabies prevention

- Animal Rabies Control
- Human Rabies Control
  - Post-exposure prophylaxis (PEP) – for exposed individuals
  - Pre-exposure prophylaxis (PrEP) – before exposure, to high risk individuals

FAQFAQFAQFAQ

Frequently Ask Questions

Animal Bite Management

Specific Guidelines

Do not delay initiation of PEP regardless of interval between exposure and consultation

- Increase the risk of rabies
- Delay has been associated with treatment failure

There are no absolute contraindications to rabies PEP

- Patients allergic to a specific vaccine/RIG or its components shall be given the alternative vaccine/RIG
- Pregnancy and infancy shall NOT be contraindications to treatment with purified cell culture vaccines (PVRV, PCECV) and RIG.

Special conditions:

- hematologic conditions where IM injection is contraindicated shall receive rabies vaccine by ID route
- chronic liver disease and those taking chloroquine, and systemic steroids – give standard IM regimen as the response to ID regimen is not optimum for these conditions
- Immunocompromised (those with HIV infection,cancer/transplant patients, patients on immunosuppressive therapy etc.) shall be given vaccine using **standard IM regimen and RIG for both Category II and III exposures**

Post-Exposure Prophylaxis (PEP)

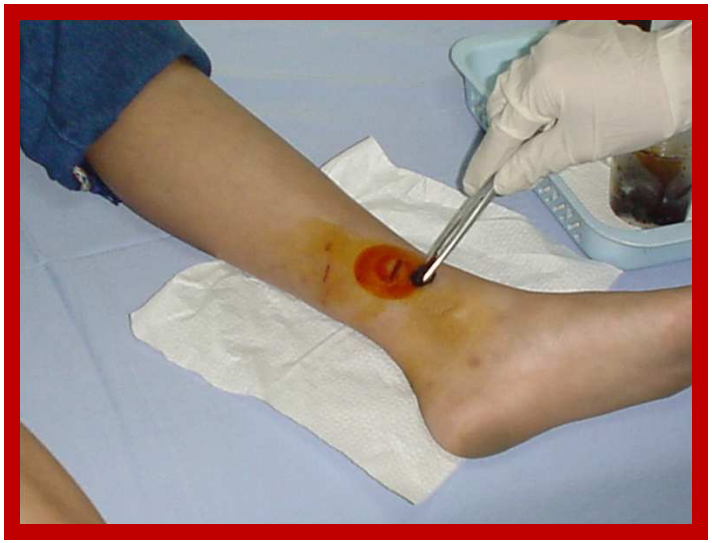
- **Components:**
  - Local wound care
  - Categorization of exposure
  - Immunization
    - Active immunization
    - Passive immunization

What can be done?

- Emphasize the importance of wound care
  - As much as 40% of rabies infection rate can be reduced by energetic wound cleaning

Kaplan MM, Cohen D, Koprowski H, et al Studies on the local treatment of wounds for the prevention of rabies. Bull WHO 1962;26:765-75

Wash with soap and water



Apply antiseptic

Categorization of Exposure

Category 1

- Feeding/touching an animal
- Licking of intact skin (with reliable history and thorough physical examination)
- Exposure to patient with S/Sx of rabies by sharing of eating or drinking utensils
- Casual contact to patient with S/Sx of rabies (talking, visiting, feeding, routine health care delivery)

Category 2

- Nibbling of uncovered skin w/ or w/o bruising/hematoma
- Minor scratches/abrasions w/o bleeding
- Minor scratches/ abrasions which are induced to bleed

Category 3

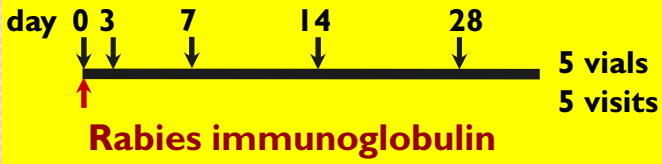
- Transdermal bites (puncture wounds, lacerations, avulsions, deep abrasions) or scratches with spontaneous bleeding
- Licks on broken skin*
- Contamination of mucous membranes (eyes, oral/nasal, genital/anal mucous membranes) with saliva
- Exposure to a rabies patient through bites, contamination of mucous membranes or open skin lesions with body fluids through splattering, through mouth-to-mouth resuscitation
- Handling of infected carcass or ingestion of raw infected meat
- All Category II exposures on head and neck area

WHO Recommended

Rabies Post-Exposure Regimens

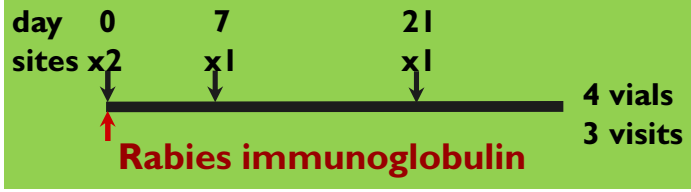
1 Essen

Standard WHO intramuscular regimen
one dose i.m. (1.0 or 0.5 ml) into deltoid



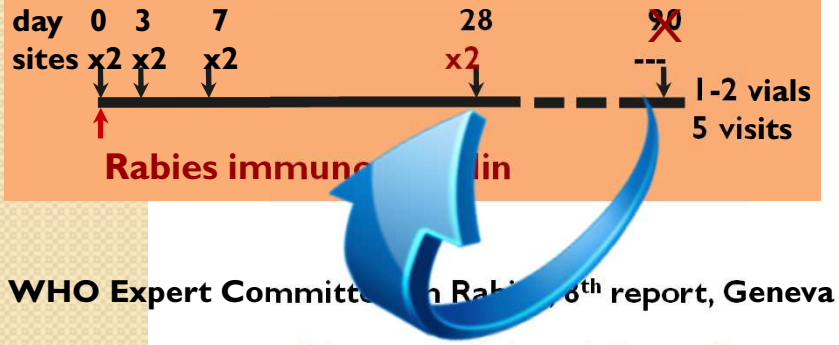
2 Zagreb

Reduced multisite intramuscular regimen (2-1-1)
one dose i.m. (1.0 or 0.5 ml) into deltoid



3 Updated Thai Red Cross

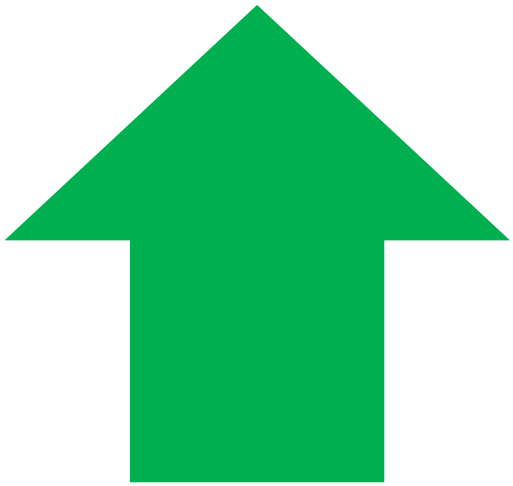
2-site intradermal regimen (2-2-2-0-2)
0.1 ml i.d. per site



WHO Expert Committe n Rab 8th report, Geneva 1992

Post-exposure Prophylaxis

Decision for day28/30 dose for both Category 2 and 3 ?

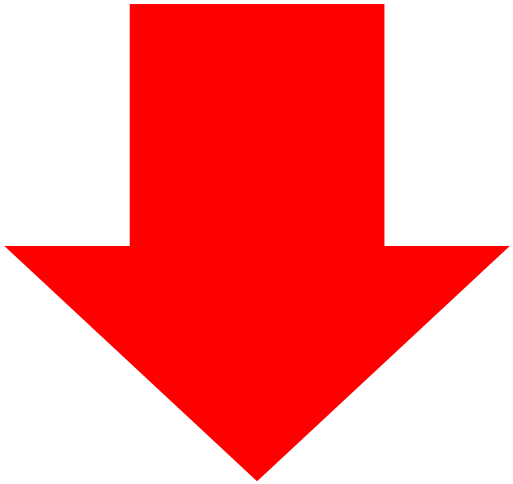


Biting animal is laboratory proven to be rabid

Biting animal is killed /died without lab testing

Biting animal has signs and symptoms of rabies

Biting animal is not available for observation for 14 days



- biting animal is alive AND remains healthy after the 14-day observation period, OR
- biting animal died within the 14 days observation period, confirmed by veterinarian to have no signs and symptoms of rabies and was FAT-negative

FAQ # 1

If the patient had received 4 doses of antirabies vaccine (D0, D3, D7, D14) after bitten by a dog, can this be considered as pre exposure doses? Such that if the patient is bitten again, will 2 doses of antirabies vaccine sufficient?

FAQ # 2

After 3 doses of schedule antirabies vaccine (for category2) Unluckily, the child was bitten again, this time on the face. Should you give Rabies IgG or just proceed with the 4th dose (D14)?

PEP schedule of previously immunized bite patient

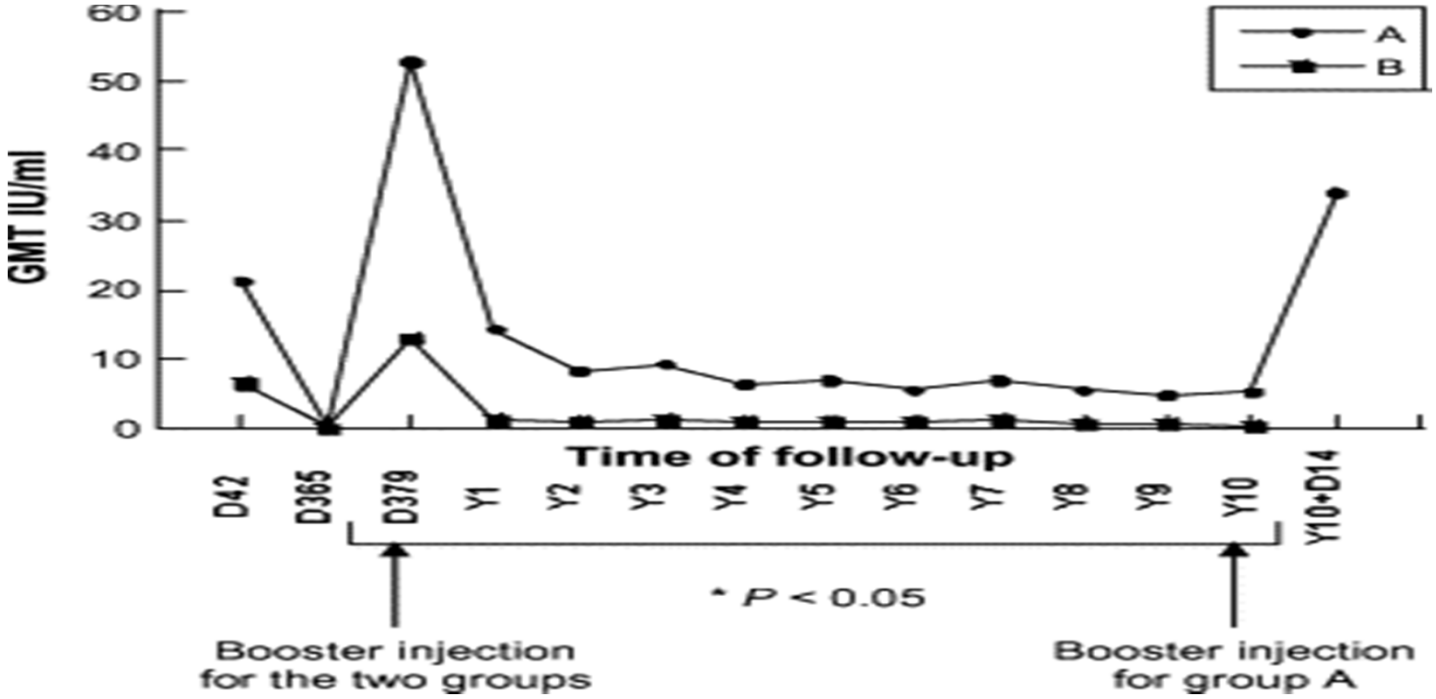
PrEP/PEP History (***Regardless of type of TCV and route of administration in previous PrEP/PEP***)	**GIVE RIG**	**Management**
Patient received the complete pre-exposure prophylaxis on Days 0, 7 and 21/28 OR Patient received at least Days 0, 3, 7 of ID/IM dose using TCV s	No	Give 0.1 ml ID dose at 1 site each on Day 0 and Day 3 or 1 vial IM dose on day 0 and day 3
Patient did not complete the 3 doses of PrEP OR Patient received only 1 or 2 ID/IM dose of the PEP	Give if indicated	Give full course of PEP

*New Guidelines on the Management of Rabies Exposures_AO 2014

FAQ # 3

What is the duration of protection after 3 full dose of pre exposure or 5 doses of post exposure anti Rabies vaccine?

Immunogenicity and booster efficacy of pre-exposure rabies vaccination



Levels in geometric mean antibody titers (GMT) from day 42 to year 10 after the primary vaccination protocol in group A and in group B. Primary vaccination protocol: vaccine injected either on day 0 and day 28, or on day 0, day 7 and day 28;

C. Strady, et.al Immunogenicity and booster efficacy of pre-exposure rabies vaccination. Transactions of the Royal Society of Tropical Medicine and Hygiene. Volu,e 103, Issue 11, 2009,1159-1164

Persistence of RVNA after PEP

TABLE 1. GMT and SCR characteristics

Time point after primary immunization	No. of patients	Range of titers (IU/ml)	GMT (IU/ml)	Seroconversion rate (%)
Day 0	195	<0.5		0
Day 7	195	0.2–14.5	0.56	41.2
Day 14	195	1.7–23.7	8.87	100
Day 45	195	2.9–35.0	16.13	100
Yr 1	183	0.3–19.5	1.79	90.5
Yr 2	177	0.2–17.2	1.44	60.5
Yr 3	174	0.1–13.1	1.21	49.1
Yr 4	171	0.0–11.0	0.99	41.5
Yr 5	168	0.0–10.2	0.81	34.0
Yr 5 + day 14	168	1.3–45.2	15.22	100

Zhang, X. et.al. Persistence of Rabies Antibody 5 Years after Postexposure Prophylaxis with Vero Cell Antirabies Vaccine and Antibody Response to a Single Booster Dose; CLINICAL AND VACCINE IMMUNOLOGY, Sept. 2011, p. 1477–1479 Vol. 18, No. 9

Duration of Protection

- Long-lasting immunity against rabies depends on immunological memory, which can be demonstrated by a rapid (anamnestic) antibody response to a booster dose
- Anamnestic responses following booster doses have been observed even 21 years after primary vaccination
- Long-lasting immunity against rabies is achieved regardless of route of immunization (IM or ID) and follows pre-exposure as well as post-exposure immunization
- Due to the long duration of protection, regular booster doses of the vaccine are not recommended following a completed pre-exposure or post-exposure series except for certain groups at continual, frequent or increased risk

Updated WHO position paper on rabies vaccines. Published in WER on 6 August 2010

FAQ #4

If there was a lapse on the schedule of administration, do we have to repeat the whole series?

Delay in second (i.e. day 3) dose

- If ***delay is 1-2 days*** from day 3 schedule (i.e. day 4-5 from start of vaccination) - day 3 dose shall be given upon visit and follow the original schedule of day 7 and 28.
- If ***delay is 3-4 days*** from day 3 schedule (i.e. days 6-7 from start of vaccination) - day 3 dose shall be given upon visit, adjust succeeding doses (day 7 and 28) according to the prescribed interval.
- If ***delay is > 4 days*** from day 3 schedule (i.e. beyond day 7 from start of vaccination) -a new course shall be restarted.

Delay in third (i.e. day 7) dose

- If ***delay is ≤7 days*** from day 7 schedule (i.e. days 8-14 from start of vaccination) - day 7 dose shall be given upon visit, give day 28/30 dose as originally scheduled.
- If ***delay is >7 - 14 days*** from day 7 schedule (i.e. days 15 to 21 from start of vaccination)- day 3 dose shall be repeated and revised according to the prescribed interval.
- If ***delay is > 14 days from day 7 schedule*** (i.e. beyond day 22 from start of vaccination) -a new course shall be restarted.

Delay in fourth (i.e. day 28) dose

- Give day 28 dose upon visit; this shall be considered as a booster.

Intramuscular regimen

- Delay in fourth (i.e. day 14) dose

  Day 14 dose shall be given upon visit and give day 28 dose after two weeks.

- Delay in fifth (i.e. day 28) dose:

  Day 28 dose shall be given upon visit.

NO NEED TO GIVE RIG IF ALREADY GIVEN

FAQ # 5

If the initial dose of antirabies vaccines was given as intradermal, can the subsequent doses be given as IM

Shifting of Routes of Administration

- No immunogenicity studies have been done regarding change in route of vaccine administration (i.e. shift from IM to ID or vice versa),
- shifting from one regimen to another shall NOT be recommended.
- As much as possible the initial regimen shall be completed.
- In extreme circumstances that shifting has to be done from IM to ID regimen or vice versa, restart from day 0 using the new regimen.

New Guidelines on the Management of Rabies Exposures_AO 2014

Interchangeability of Vaccine Brand

- Shifting of vaccine brand shall not be recommended but may be warranted in the following circumstances, provided that it is one of the WHO recommended cell culture vaccines:
  - Hypersensitivity reaction such as generalized rash, anaphylaxis, severe generalized pruritis, severe local reaction at injection site(swelling of entire upper arm).
  - Unavailability of the initial vaccine used.

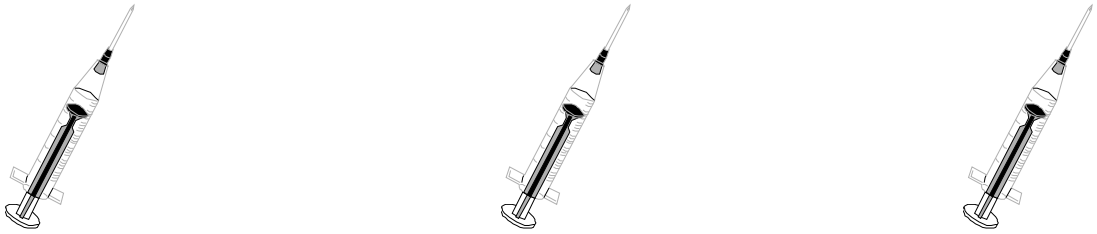
New Guidelines on the Management of Rabies Exposures_AO 2014

FAQ # 6

After a complete dose of pre-exposure antirabies vaccine, the child was bitten by a dog 3 weeks after. What should be given to this patient?

Pre-exposure schedule

Day 0 **Day 7** **Day 21/28**



IM dose = 0.5 ml PVRV or 1.0 ml PCECV

ID dose = 0.1 ml PVRV, PCECV

Into the deltoid muscle or anterolateral thigh in young infants

Pre-exposure prophylaxis

- Benefits
  - The need for passive immunization product (RIG) is eliminated
  - PEP vaccine regimen is reduced from five to two doses
    - The cost of PEP is reduced
  - Protection against rabies is possible if PEP is delayed
    - Particularly important to persons who travel to rabies-endemic areas where RIG may not be readily available

Summary

- Rabies remains to be a public health problem
- 100% fatal but 100% preventable
- What can be done to continuously eliminate rabies
  - Provision of vaccine for PreP and PEP
  - Follow PEP guidelines strictly -
  - Guidelines change over time so it is important to remain updated

THANK YOU!