



# KOMITE PENASIHAT AHLI IMUNISASI NASIONAL (Indonesian Technical Advisory Group on Immunization)

DECREE No. 904/MENKES/SK/VII/2010

SECRETARIAT : JL. PERCETAKAN NEGARA 29 JAKARTA PUSAT

TLP/FAX. 424-9024 – 425-7044

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## Evaluation of Intradermal Rabies Vaccination

### Background

A follow up of "Workshop on Intradermal Method of Rabies Vaccination", on the 6-9 May 2010, as per request from Bali Health Authority through the letter no : 443.33/1707/Dinkes regarding recommendation for Intradermal Anti Rabies vaccination. This request was made due to high number patients with dog bites that came to Rabies Center Sanglah Hospital, Denpasar.

The Director General of Diseases Control and Environmental Health (Direktur Jenderal PP&PL) on the 14 May 2010 sent a report to Minister of Health regarding workshop on management of intradermal rabies vaccination that was conducted on 6-9 May 2010.

There is also a letter from Director of PPBB, to experts from National Technical Advisory Group on Immunization (TAG), dated 31 May 2010 No PM.01.13/IV.3/975/2010, regarding the recommendation on intradermal administration method of anti rabies vaccine to human.

### Evaluation by Indonesian Technical Advisory Group on Immunization

#### 1. 1.1 Global epidemiological data <sup>1</sup>

In more than 100 countries, rabies behaves as an *enzootic* disease among its animal population. Rabies among dogs is a source of an infectious disease that can cause fatality in over 3,3 million populations, especially in Asia and Africa. In India, there are 20.000 deaths/year or 2 per 100.000 people/year. In Africa, it is estimated there are ± 24.000 deaths/year or 4 per 100.000 people/year. Rabies most commonly observed among children below 15 years of age and 30-50% children age 5-14 years receive post exposure prophylactic vaccination. It is also estimated that more than 10.000.000 people receive post exposure prophylactic vaccination every year, with highest numbers are reported in China and India.

#### 1.2 Reported experience from Thailand <sup>2</sup> and India <sup>3, 4, 5)</sup>

Since 1984 Thailand has applied the Intradermal (ID) method of Anti Rabies Vaccination, with two site method regiment of 2 – 2 – 2 – 0 – 2 . in India since 2006, the Drug Controller General India (DCGI) recommended administration of VAR (Anti Rabies Vaccine) ID if there are more than 50 patients visits/day, with available trained staff, and good cold chain management.

#### 2. Rabies situation in Indonesia <sup>6)</sup>

- At present rabies is endemic in 24 provinces (9 provinces are rabies free : West Kalimantan, Bangka Belitung, Jakarta, Central Java, Yogyakarta, East Java, West Nusa Tenggara, Papua and West Irian Jaya)
- There are two provinces that reported new cases from: Bali (2008) and Riau Islands (2009)
- Cases of animal bites that are potentially transmit rabies (*Kasus Gigitan Hewan Penular Rabies/GHPR*) increased in 2009 due to outbreak in Bali



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Table 1. Rabies situation in Indonesia (16 June 2010)

No.	Province	Total				No.	Province	Total			
		KG	PET	L	SP			KG	PET	L	SP
1	NAD	0	0	0	0	14	North Sulawesi	0	0	0	0
2	North Sumatera	1483	1304	23	7	15	Gorontalo	65	22	0	0
3	West Sumatera	815	480	4	83	16	Central Sulawesi	121	67	0	8
4	Riau	491	397	0	18	17	Southeast Sulawesi	66	58	0	0
5	Riau Islands	1	0	1	0	18	South Sulawesi	68	39	0	0
6	Jambi	197	114	1	16	19	West Sulawesi	0	0	0	0
7	South Sumatera	50	26	2	2	20	South Kalimantan	0	0	0	0
8	Bengkulu	206	136	0	0	21	Central Kalimantan	317	186	0	1
9	Lampung	76	76	1	0	22	East Kalimantan	0	0	0	0
10	Banten	36	30	0	2	23	North Maluku	0	0	0	0
11	West Java	11	3	1	0	24	Maluku	182	114	1	0
12	Bali	23637	18075	35	25	<b>Total</b>		<b>28839</b>	<b>21685</b>	<b>76</b>	<b>181</b>
13	Eastern Nusa Tenggara	1017	558	7	19	<b>Percentage (%)</b>			<b>75.19</b>	<b>0.264</b>	

Legend: KG (Cases of animal bite), PET (*Post Exposure Treatment*), L (Lyssa), SP (Suspected Positive)

Source : Sub Directorate of Zoonosis, 21 June 2010

### 3. Intradermal study experience in Indonesia <sup>7)</sup>

Intradermal Study in Indonesia among total of 124 subjects, with results as follows; Immune response post intradermal anti rabies vaccination (55 cases) compared to intramuscular anti rabies vaccination in 69 cases. Antibody titer was found in 33 subjects, and PTSL among 36 subjects, among subjects with animal bites that are potentially rabies in community.

It is concluded that the antibody titer and percentage of T cell cytotoxic (PLSTCL= Percentage of specific Lysis by T cytotoxic Lymphocyte cell) after VAR ID administration is equally good compared to VAR IM (intramuscular) post immunisation on day 7, 21 or 28, although anti rabies antibody response after VAR ID 7 days post immunisation has higher titer compared to VAR IM.

### 4. Global policy regarding rabies vaccine

#### 4.1 Guideline : WHO position paper 2007

In certain countries where rabies is a health problem, rabies vaccination is very much required. However, modern rabies vaccine produced from cell culture (CCV = cell cultured vaccine) is expensive and it is limited in supply, thus an intradermal regimen which is also cost-saving since it reduces CCV antigen dose usage, is an alternative regimen. Intradermal regimen can be administered pre and post exposure.

#### 4.2 Global Situation:

Since 1991 WHO has recommended rabies vaccination with intradermal method for both pre and post exposure conditions. Developing countries that already have utilized intradermal regimen for post exposure prophylaxis are India, The Philippines, Sri Lanka and Thailand.



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## 5. Rabies vaccine administration procedure

### 5.1. Rabies vaccine

Currently in Indonesia *Purified Vero Rabies Vaccine* (PVRV), produced by PT. Sanofi-Pasteur (Verorab®) is being utilized for the immunization program.

#### 5.1.1 VAR administration method

##### **Intramuscular Regimen as per WHO Standard** <sup>8,9)</sup>

Since 1991 VAR administration method in Indonesia follows the WHO standard according to Zagreb method, that is 2 – 1 – 1 method (2 doses @ 0,5 cc on day 0; 1 dose @ 0,5 cc on day 7 and 1 dose @ 0,5 cc on day-21) injected intramuscularly. This method simplifies and shorten the schedule and number of visits. Vaccine is injected in the deltoid region of upper arm in adults, and antero lateral part of thigh in children. Intramuscular injection is not recommended to be administered at the gluteus (buttock) area since it produce lower anti rabies antibody and lower rates of seroconversion.

This Zagreb method is commonly used in several countries such as Japan, Singapore, Malaysia, and several European and American countries. However there are countries that also use both methods intramuscular and intradermal methods at the same time, such as India, Thailand, The Phillipines and Srilanka (Source : Workshop on Intradermal rabies vaccine administration in Bandung 6 – 9 May 2010)

Based upon results of studies conducted in some other countries as well consideration of high cost of standard intramuscular regimen, it was recommended to administer VAR through intradermal method. Several conditions need special attention: The dose of intradermal is 0,1 ml. The Intradermal vaccine can be given as two-sites intradermal regimen (2-2-2-0-1-1) as injection on day 0, 3, 7, and one one each injection on day 28 and on day 90

##### **Intradermal Injection Regimen** <sup>10,11)</sup>

Intradermal method as per WHO recommendation is administered through 2 – 2 – 2 – 0 – 2 method (2 doses @ 0,1 cc on day 0; 2 doses @ 0,1 cc on day 3; 2 doses @ 0,1 cc on day 7, 0 dose on day 14; and 2 doses @ 0,1 cc on day 28). This method is considered cost saving since complete series of VAR requires vaccine volume of 0,8 cc, while the intra muscular method needs of 2 cc. Reports from several publications as well WHO report showed that both methods provide effective protection for animal bites that can potentially transmit rabies.

For the intradermal rabies immunization program in Indonesia, it is recommended the following method:

- Two-sites intradermal regimen (2-2-2-0-2)
- Dosage : dose of intradermal 1/5 0,1 ml of intramuscular dose at each injection site

Table 2. VAR post-exposure immunization schedule:

Day	0	3	7	28
Number of injections	2x	2x	2x	2x



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## 5.1.2 Vaccine storage and administration

Vaccine should be kept in temperature of 2-8 °C; diluted vaccine should be used within eight hours<sup>12)</sup>

## 5.1.3 Contra indication for intradermal administration

Should not be given to subjects that are receiving anti malaria medication: chloroquin, since this drug can reduce antibody development.

## 5.2 FDA (Badan POM) role

Food and Drug Administration agency (Badan POM) should be informed regarding change in method of VAR administration from intra muscular to intradermal for *off* label usage.

## 5.3 Preparation for intradermal implementation

- It requires trained staff to administer the vaccine intradermally
- A SOP (Standard Operating Procedure) for grading location and degree of severity of bite.
- Calculation regarding index effectivity of vaccine utilization

## 5.4 National Institute of Health Research and Development (Badan Lit bang kes) role

Along with intradermal rabies vaccine new regiment pilot project, it is necessary to conduct:

- *immunogenicity* and *reactogenicity* of intradermal regiment (through sampling method with numbers that fulfill the study criteria).
- CEA (*cost effective analysis*) Study

## 6. Monitoring and Surveillance of post Immunization adverse reaction conditions (VAERS/KIPI)

Monitoring and evaluation will be conducted through both active as well passive surveillances, by the Dir Gen CDC Sub Dir of Immunization (Ditjen PP&PL cq Subdit Imunisasi) and FDA/BPOM. It is important to strengthen the post immunization VAERS monitoring for the intradermal regiment especially for the local reaction.



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## Recommendation

1. To follow the WHO standard and experiences from other countries as well the Indonesia study experience, the intradermal rabies vaccination can be given with: *two-sites* intradermal regimen (2-2-2-0-2).
2. As a demonstration project, it is recommended VAR administration method to be adjusted with the number of visits (rabies cases), whenever there are high number of visits >50 cases, Intradermal rabies vaccine to be administered such as in Bali Province, chosen as rabies center at Sanglah Hospital.
3. To continue the immunogenicity study for pre and post intradermal rabies vaccination and CEA study.
4. To strengthen the *Post Marketing Surveillance for VAER* KIP anti rabies vaccine periodically

Jakarta, 30 June 2010

Chairman of Indonesian Technical Advisory Group on Immunization

Signature

**Prof. Dr. Sri Rezeki S Hadinegoro, dr., Sp.A(K)**

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