

Rabies

Pre-exposure prophylaxis

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Rabies



- **Most important viral zoonosis**
- **Acute viral encephalitis transmitted through the bite of an infected animal**
 - **No effective cure and the prognosis for patients with clinical rabies is almost certain death**
- **Ranks 11th among the major killer diseases (WHO)**
- **60,000 human deaths worldwide**
 - **30,000 in Asia; 24,000 in Africa (90 % of world estimate)**
- **Around 10 million people exposed annually**

Vaccine preventable infection!!!



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Rabies: Special Features

- Zoonosis - control of human rabies depends on control of animal rabies
- 100 % fatal; no effective Tx available
 - Best example of illness where prevention is better than cure
- Vaccine can be given before (pre-exposure) or after an exposure (post-exposure)
 - Exact exposure can be pinpointed in most cases
- Rabies vaccine already in the national control program
 - For post exposure prophylaxis
 - Pre-exposure prophylaxis – for implementation



Rabies in Asia

- Over 30,000 die every yr
- One Asian dies from rabies every 15 minutes
 - 50% likely to be a child under 15 years
- More than 3 B people in Asia are potentially exposed to dog rabies
- Over 10 M PEPs annually
 - 800 PEPs per hour
 - 70 % of worldwide PEP
- Some countries still using NTV

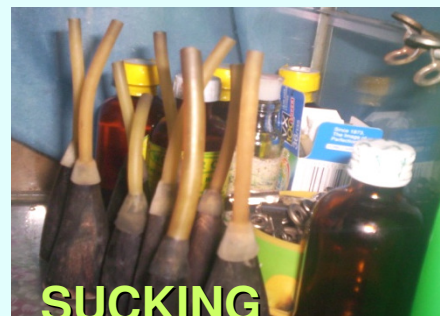


Human Rabies and Post-exposure Prophylactic Treatments, Asia, 2004

Country (Source: WHO World Survey of Rabies www.who.int/rabnet)	Deaths	Rate/million	Post-exposure Treatment	Rate/mil
India	17,000	16.7	2,500,000	2,568
Pakistan	2,490	17	69,000	469
Bangladesh	1,550	12	60,000	455
Myanmar	1,100	23	5,000	102
China	2009	1.6	7,000,000	5,400
Philippines	248	3.3	102,148	1,338
Indonesia	40	0.2	8,800	43
Sri Lanka	76	4	80,000	4,200
Thailand	26	0.41	200,000	3,178
Vietnam	30	0.38	635,000	8,105
Nepal	44	2.17	25,000	1,085
Cambodia	2	0.80	12,000	1,071
Lao People s Democratic Republic	2	1.26	3,000	540
Mongolia	2	0.80	62	25
TOTAL	24,609	6.5	10,392,010	Approx 2,000

Rabies in the Philippines

- Domestic dog is the main vector
- Rabies is a reportable disease
- Special features
 - Traditional Medicine
 - Cultural practices/beliefs - eating dog meat, free ranging pets, fear of vaccination

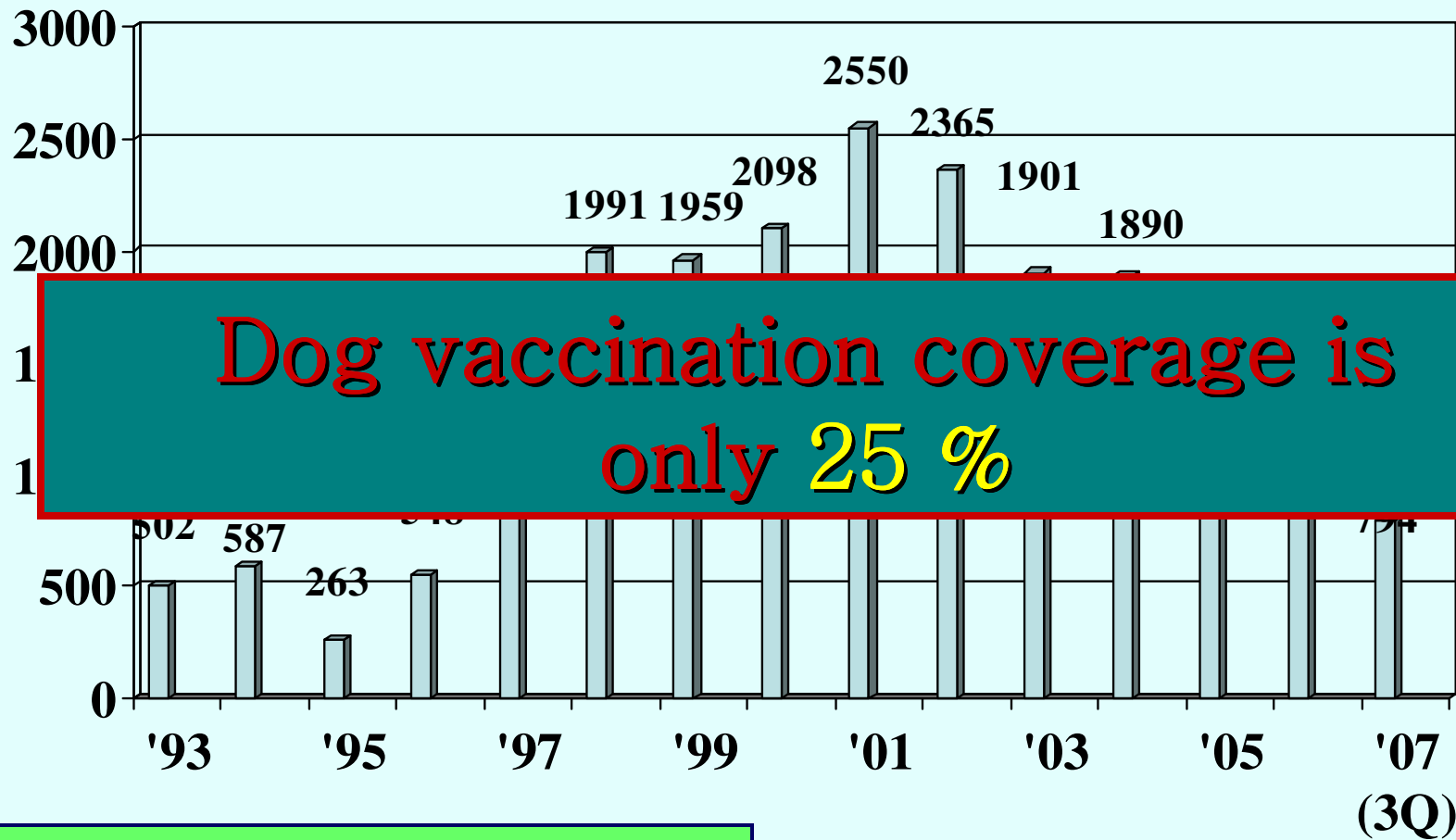


**SUCKING
APPARATUS**





Animal Rabies cases, Philippines



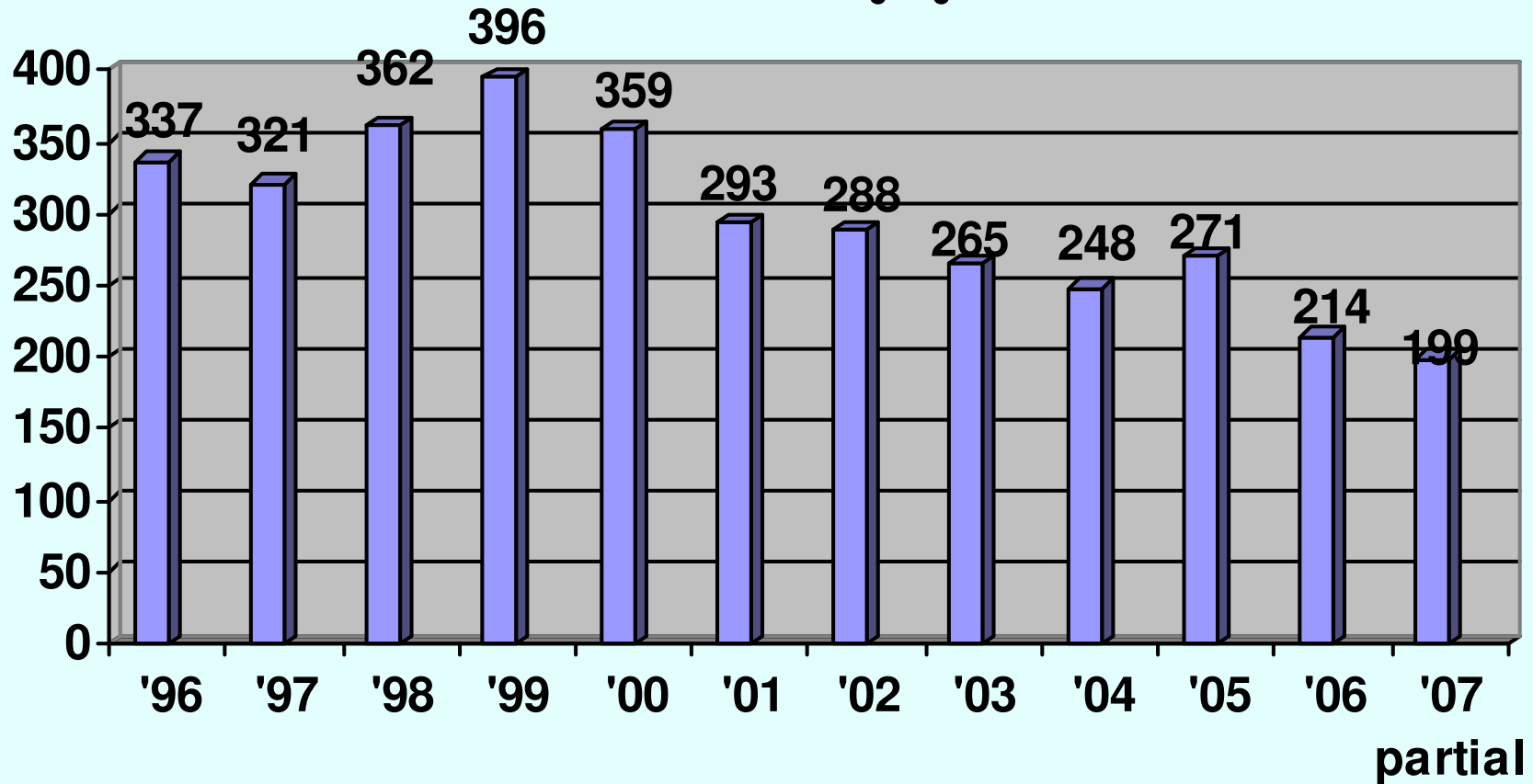
Only 17 rabies diagnostic labs serving
the whole country

DA-BAI, 2008

RABIES CASES



Human Rabies cases, Philippines



DOH, 2008



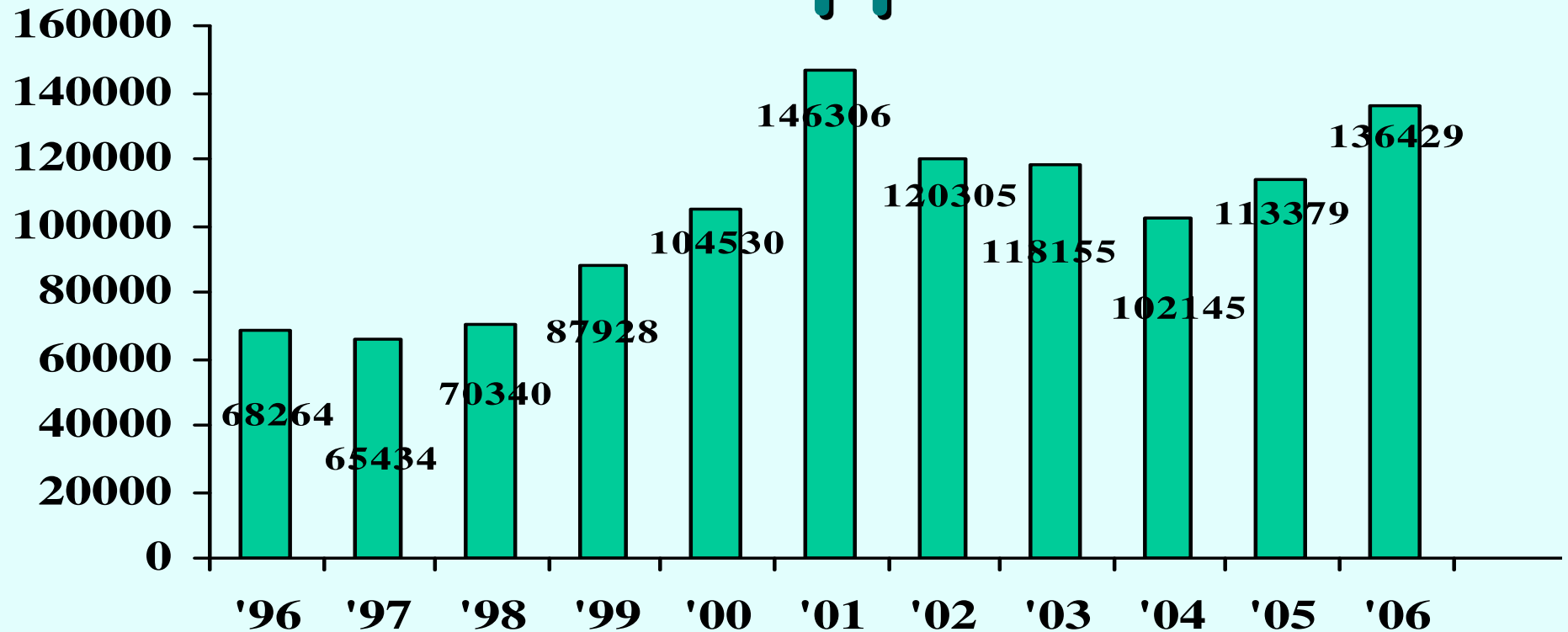
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BITE VICTIMS

Animal Bite cases, Philippines



The cost of the Tx of bite victims seeking PEP every year is a significant economic burden



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Rabies Prevention and Control

- **Animal rabies control is the cornerstone of any rabies control program**
 - **Dog vaccination:**
 - **Decreases incidence of dog rabies**
 - **by 70 % after the 1st campaign**
 - **by 95 % after the 2nd campaign**
 - **Decreases incidence of human rabies**
 - **Decreases incidence of bites**
 - **Must be done annually**
 - **Must be coupled with dog population control measures**
- Cleaveland et al., Vaccine 2003**
- **Control program headed by DA in coordination with the DOH, DepEd, DILG**
 - **Rabies is not a priority disease for DA**



"Anti-Rabies Act of 2007"

- Republic Act No. 9482
- An Act providing for the control and elimination of human and animal rabies
- Signed into law on May 25, 2007
- **Provides for free routine immunization or Pre-Exposure Prophylaxis of schoolchildren aged five to fourteen**
 - in areas with a high incidence of rabies (IR > 2.5/M pop)



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



Pre-exposure prophylaxis

- **Benefits**
 - **Protection against inadvertent exposure to rabies is possible**
 - Important in young children who may not report a bite
 - Bites from bats may go unnoticed due to their trivial size and painlessness
 - Unrecognized exposures may occur among cave explorers and vaccine laboratory accidents



Pre-exposure prophylaxis

- **Target population**
 - Personnel in rabies diagnostic or research laboratories
 - Veterinarians and veterinary students
 - Animal handlers, zoologists working with wildlife
 - HCW directly involved in care of rabies patients
 - Individuals directly involved in rabies control
 - Cave explorers and adventure travelers to rabies endemic areas
 - Field workers
 - **It is recommended that children also be immunized because of the increased risk and severity of animal bites in this age group**



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Basis for adding pre-exposure rabies vaccination into the national program

- **Disease burden in the country**
 - Specifically for the age group to be vaccinated
 - Human rabies cases
 - Animal bite patients
- **Immunogenicity/Efficacy**
- **Safety**
- **Cost effectiveness**



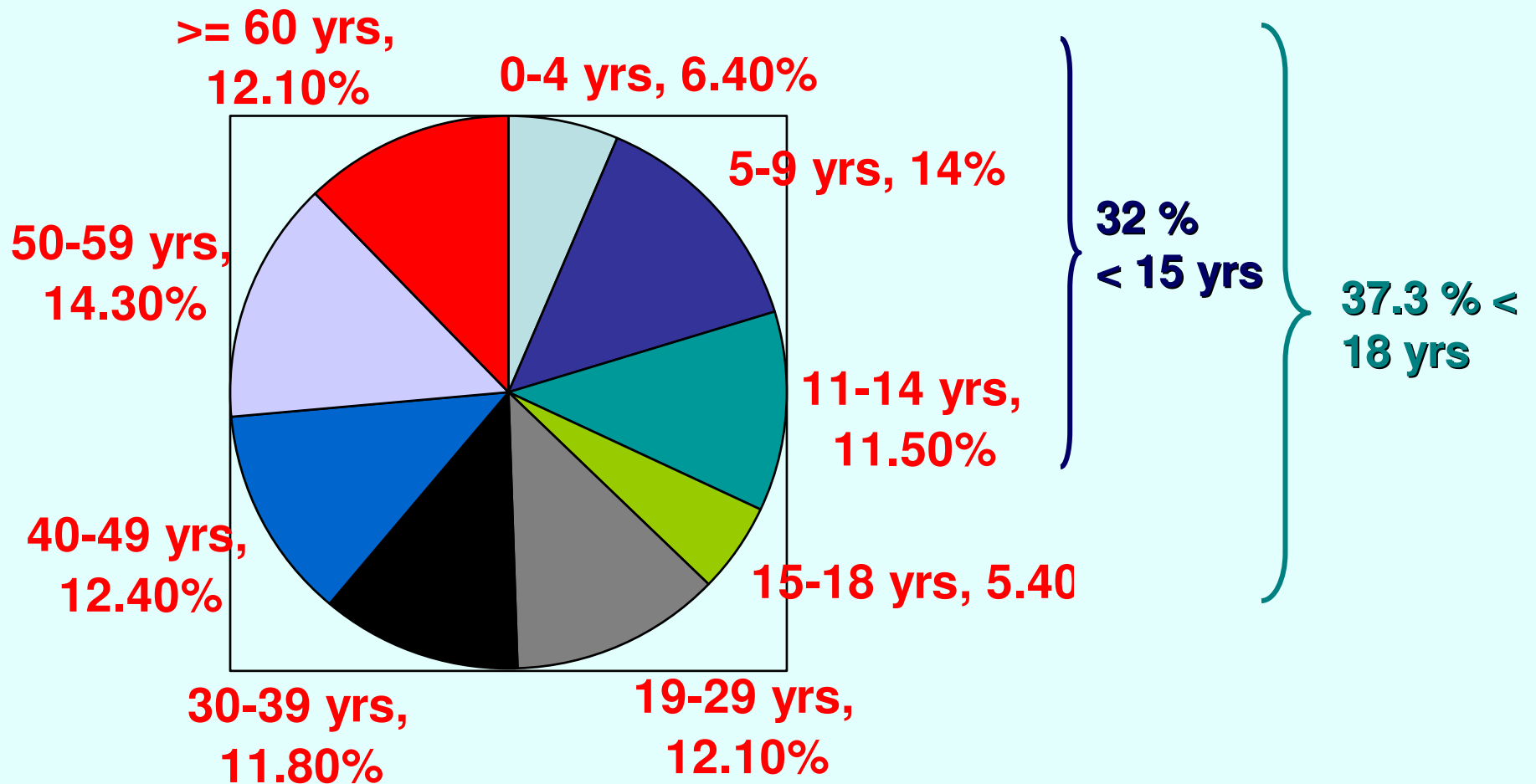
Rabies risk in children

- **Children < 15 years old - most frequently exposed age group (approx 50% of human exposures in canine rabies-infected areas)**
 - **Small size**
 - less intimidating to animals
 - prone to bites on the head and neck, vulnerable to disfiguring facial attacks including intracranial penetration
 - **More likely to be involved in provocative behavior**
 - **Fail to recognize and avoid threatening behavior**
 - **Less able to shelter themselves or escape when attacked**

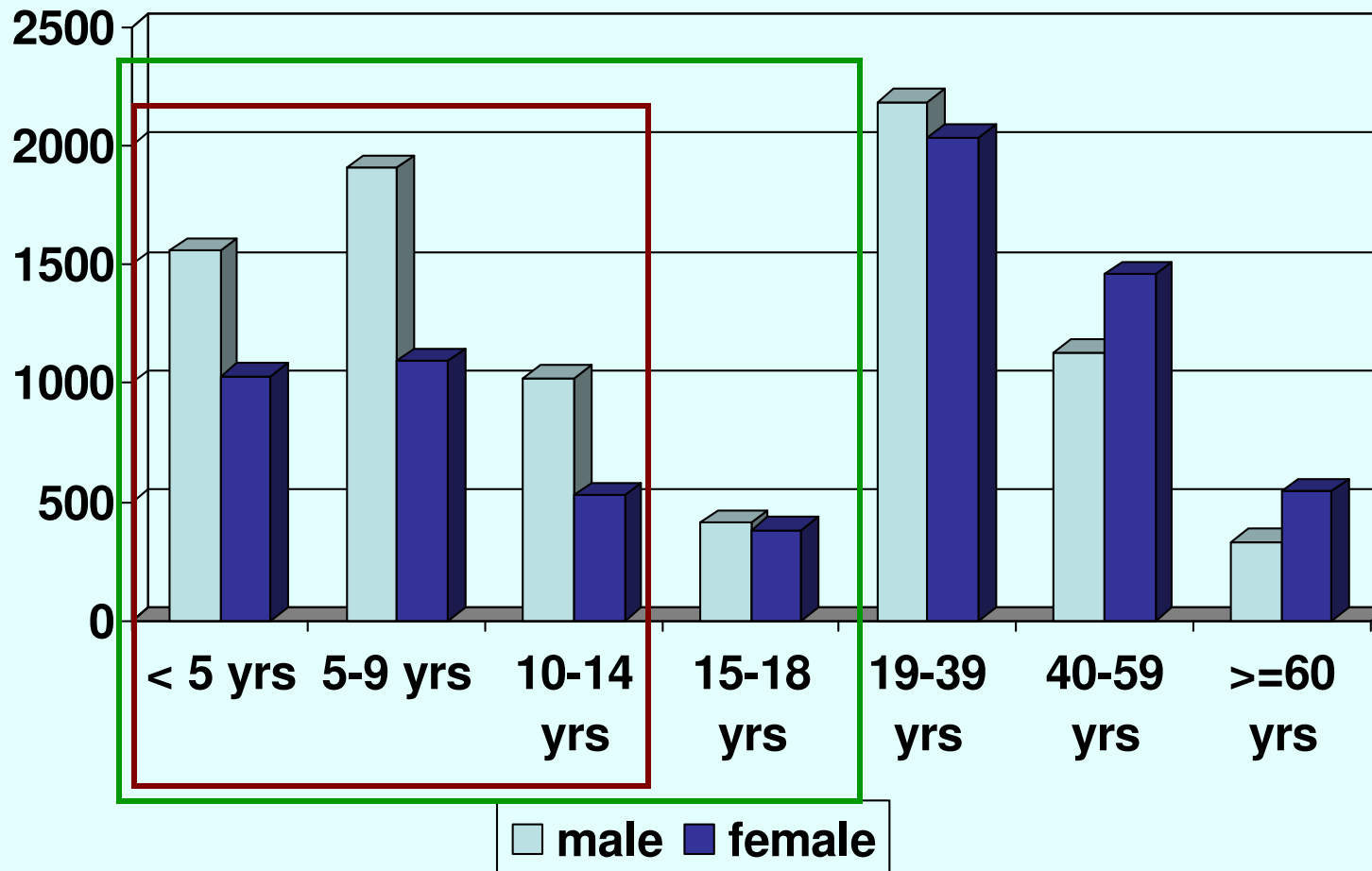




Human Rabies cases, RITM (N=314)



Animal Bite cases, RITM



- 48 % pediatric age group
- 46 % below 15 yrs
- 17 % below 5 yrs

- National data
- 50 % below 15 yrs

Efficacy

- **The efficacy of rabies vaccination has been proven in RCT of post-exposure regimens**
- **There are no RCTs on the efficacy of pre-exposure rabies vaccination:**
 - **Long incubation period of the disease**
 - **Ethical issues precluding conduct of controlled trials on rabies prevention after exposure among those given pre-exposure vaccination**
 - **No rabies cases among those with pre-exposure prophylaxis who have been re-exposed to rabies and received booster doses**

Pre-exposure rabies vaccination using 2-dose or 3-dose PCEC

- **Of 703 children enrolled:**
 - **12 children (1.7%) had an actual exposure to a suspected rabid animal**
 - **2/12 children received a primary PreP series of 3 doses**
 - **Given booster doses on days 0 and 3; no RIG**
 - **10/12 children received a primary PreP series of 2 doses**
 - **Given the full course of PEP according to the Thai Red Cross ID regimen**
- **All 12 children completed the 1-year follow-up period and are alive and healthy**

Immunogenicity

- **Indirect assessment of vaccine efficacy**
- **Different cutoffs used as correlate of protection:**
 - **WHO - Minimum level of 0.5 IU/ml**
 - **CDC - at least 0.15 IU/ml**
 - **The ability to respond to post-exposure booster immunization (not the magnitude of the Ab titer following primary immunization) which determines protection from clinical rabies**



Early report

Randomised feasibility trial of pre-exposure rabies vaccination with DTP-IPV in infants



**The Pediatric
Infectious Disease Journal**

[Home](#) | [Search](#) | [Current issue](#) | [Archive](#)

November 1998, 17:11 > Persistence of antibodies in children...

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ARTICLE LINKS:

[Abstract](#) | [References \(28\)](#) | [View thumbnail images](#)

The Pediatric Infectious Disease Journal: Volume 17(11) November 1998 pp 1001-1007

Persistence of antibodies in children after intradermal or intramuscular administration of preexposure primary and booster immunizations with purified Vero cell rabies vaccine [Original Studies]

SABCHAREON, ARUNEE MD; CHANTAVANICH, PORNTHAP MD; PASURALERTSAKUL, SATAPORN MSc; POJJAROEEN-ANANT, CHANATHEP MSc; PRARINYANUPHAB, VIPA BSc, BN; ATTANATH, PHANORTRI MSc; SINGHASIVANON, VANVAROTHAJ MD; BUPPODOM, WANTANA MD; LANG, JEAN MD, PhD

TRANSACTIONS OF THE ROYAL SOCIETY OF TROPICAL MEDICINE AND HYGIENE (1999) 93, 206-213

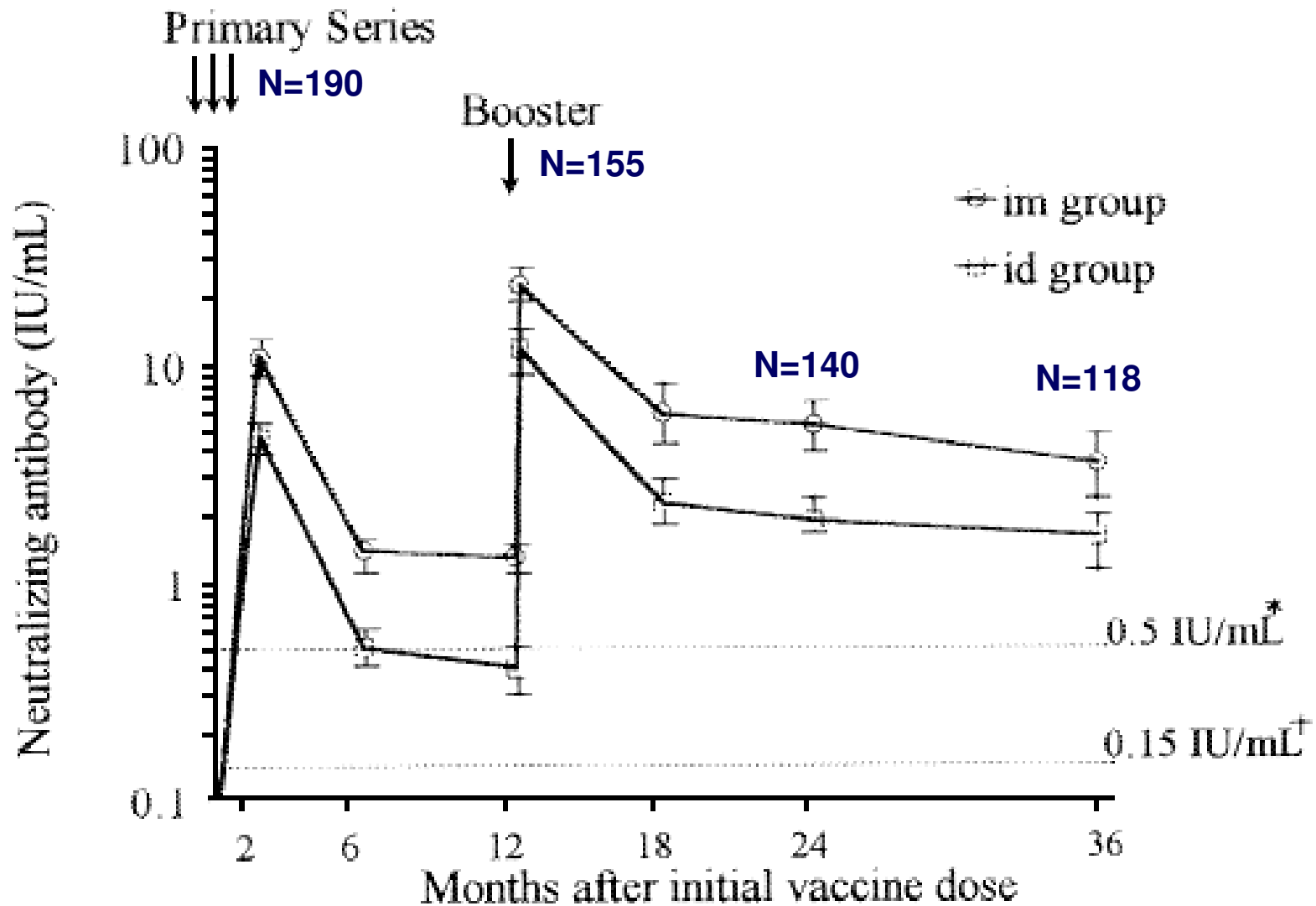
Immunogenicity and safety of low-dose intradermal rabies vaccination given during an Expanded Programme on Immunization session in Viet Nam: results of a comparative randomized trial

Jean Lang^{1*}, Duong Q. Hoa², Nguyen V. Gini², Le Thanh Tho², Nguyen C. Vien², Nicolas Rouyere³ and Remi Forrat¹ *¹Pasteur Institute, Cochin, Lyon, France; ²Pediatric Developmental Centre, Ho Chi Minh City, Viet Nam*

Pre-Exposure Rabies Vaccination Using Purified Chick Embryo Cell Rabies Vaccine Intradermally is Immunogenic and Safe

THAVATCHAI KAMOLTHAM, MD, MSc, WIRAWAN THINYOUNYONG, BSc, PHANA PHONGCHAMNARHAJ, MD, PHRAN PHRAISUWAN, MD, PAKAMATZ KHANPLOD, PhD, ANGELIKA BANZHOF, MD, AND CLAUDIUS MALERCZYK, MD

Kinetics of Ab response to PVRV after IM and ID primary series and booster



Pre-exposure rabies vaccination using 2-dose or 3-dose ID PCEC

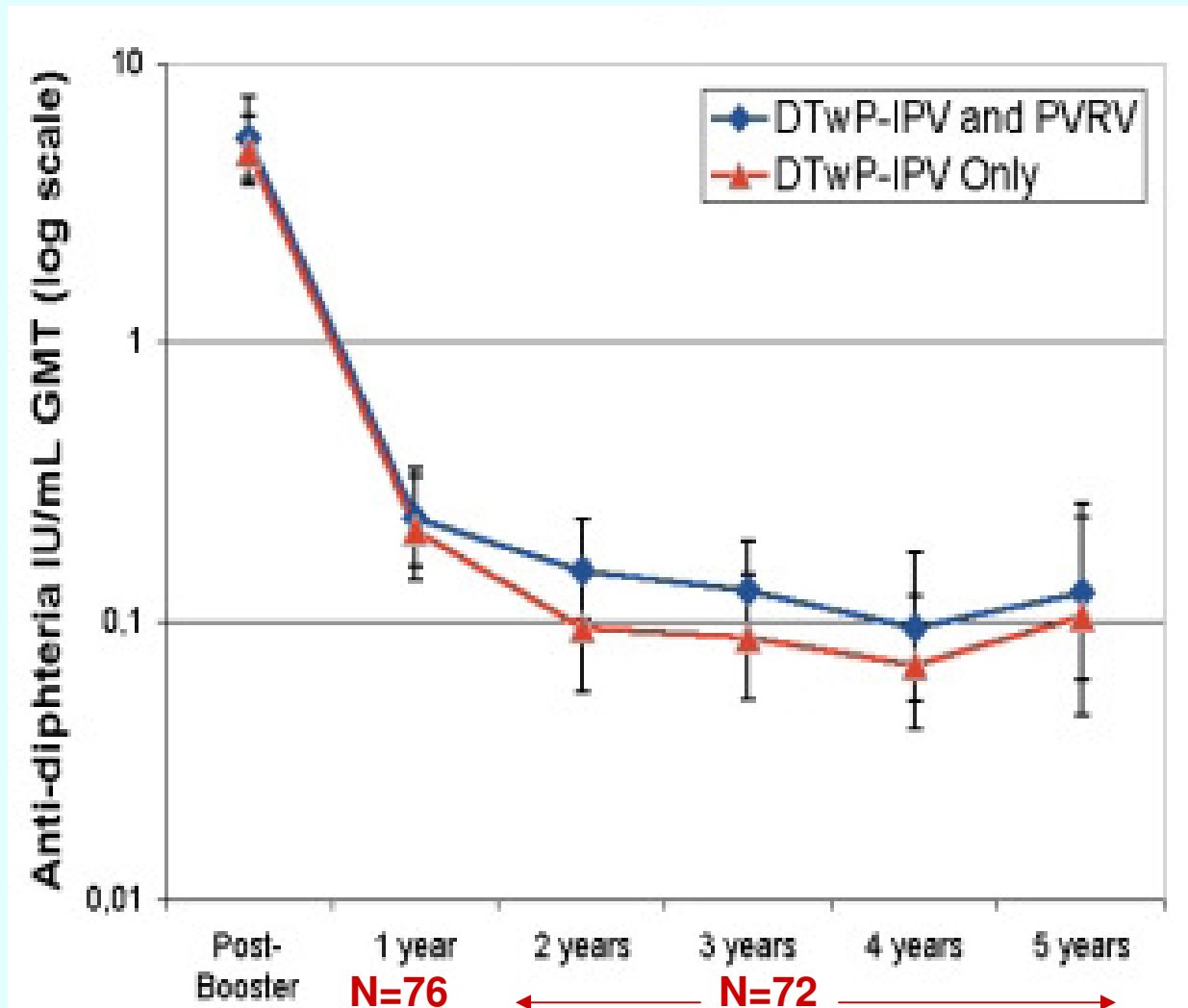
- 703 children received either of 2 regimens:

2 dose – PCEC ID on days 0 and 28 (N=84)

3 dose – PCEC ID days 0, 7 and 28 (N=63)

	Day 49 Post 1 ^o series	Day 0 Pre booster	Day 7 Post booster	Day 14 Post booster	Day 365 Post booster
2 dose regimen					
No.	43	84	81	81	77
GMT	3.5	0.11 (0.08, 0.14)	4.69 (3.79, 5.8)	10.76 (8.86,13.06)	0.65 (0.51,0.83)
% ≥ 0.5 iu/ml	98%	7%	96 %	100%	66%
3 dose regimen					
No.	30	63	58	58	59
GMT	5.0	0.33 (0.25,0.44)	10.69 (8.71,13.8)	22.12 (17.91,27.31)	2.48 (1.9, 3.23)
% ≥ 0.5 iu/ml	100%	35%	100 %	100%	93%

GMT of Anti-diphtheria Ab



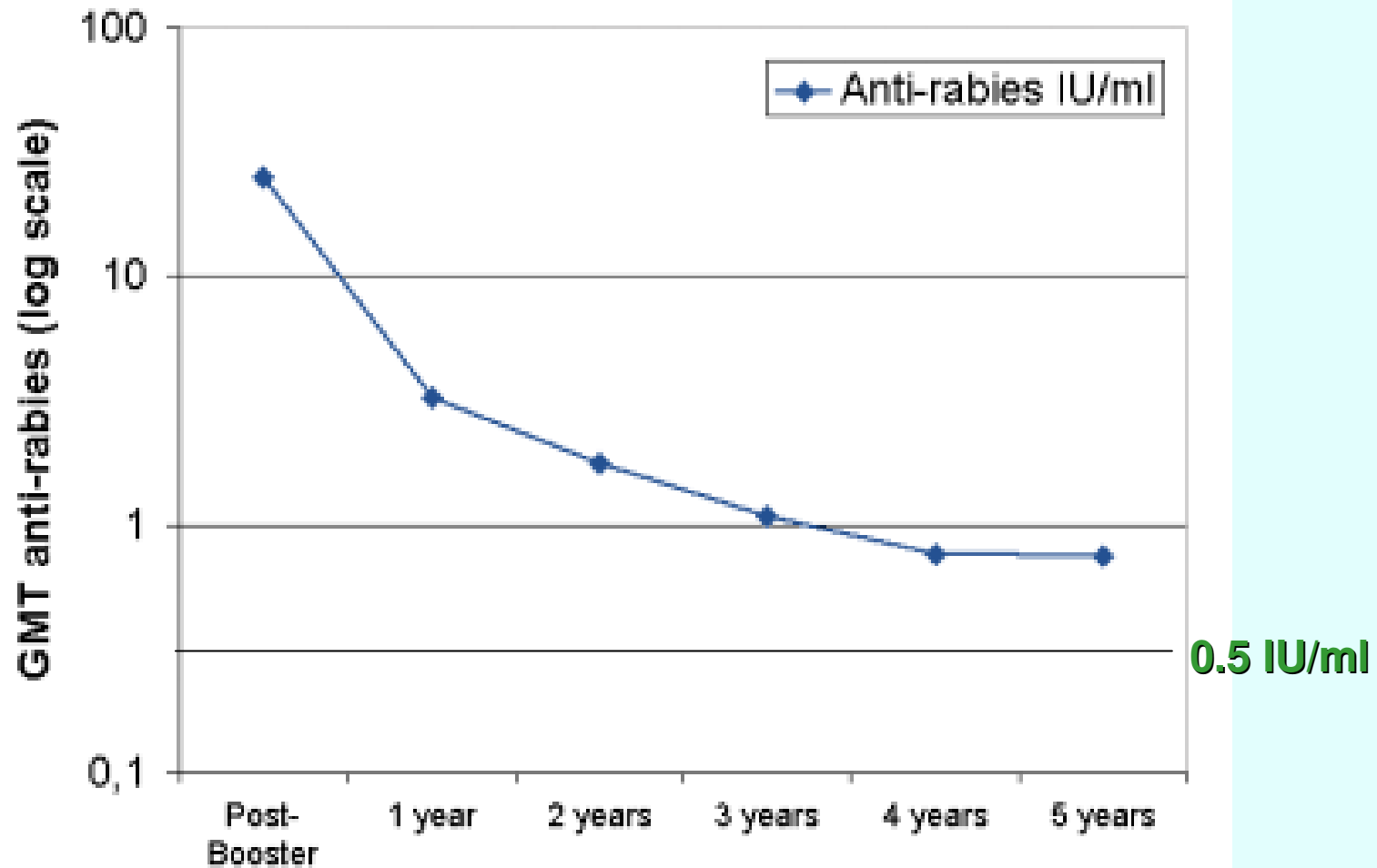
N=84

Diphtheria: ELISA ≥ 0.01 IU/mL

Lang et al, J Trop Pediatr, 1999

Lang et al, J Trop Pediatr, Nov 07

GMT of Anti-rabies Ab



Seroprotection rate **100 %** **90.9%** **89.7%** **66.7%** **64.3 %** **63.3%**

Lang et al, J Trop Pediatr, 1999

Lang et al, J Trop Pediatr, Nov 07

5-yr anti-rabies seroprotection rates in children receiving primary & booster vaccinations of DTwP-IPV & PVRV

	Pre-Boost 1	Post-Boost 1	1 yr	2 yrs	3 yrs	4 yrs	5 yrs Pre boost	Post boost 2
IM								
No.	113	103	98	92	92	91	87	85
% ≥ 0.5 IU/mL	97.5	100	100	97.9	94.8	86.5	80.4	100
ID								
No.	115	114	106	103	102	98	92	89
% ≥ 0.5 IU/mL	95.5	100	99.0	96.9	83.3	67.7	54.0	100

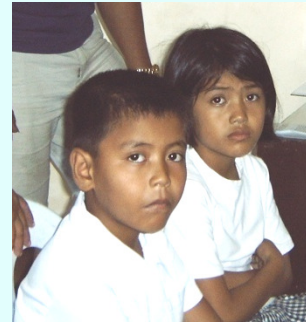
Cong Vien et al, Transac Roy Soc Trop Med Hyg, 2008

Doi:10.1016/j. trstmh. 2007.11.010

A phase IV, prospective, open-label, randomized, single center study to assess the immunogenicity and safety after pre-exposure vaccination with 2 or 3 intradermal doses of Purified Chick Embryo Cell Rabies Vaccine in healthy school children (5-9 years of age) in the Philippines

Vinluan M, Olleres A, Quiambao B.

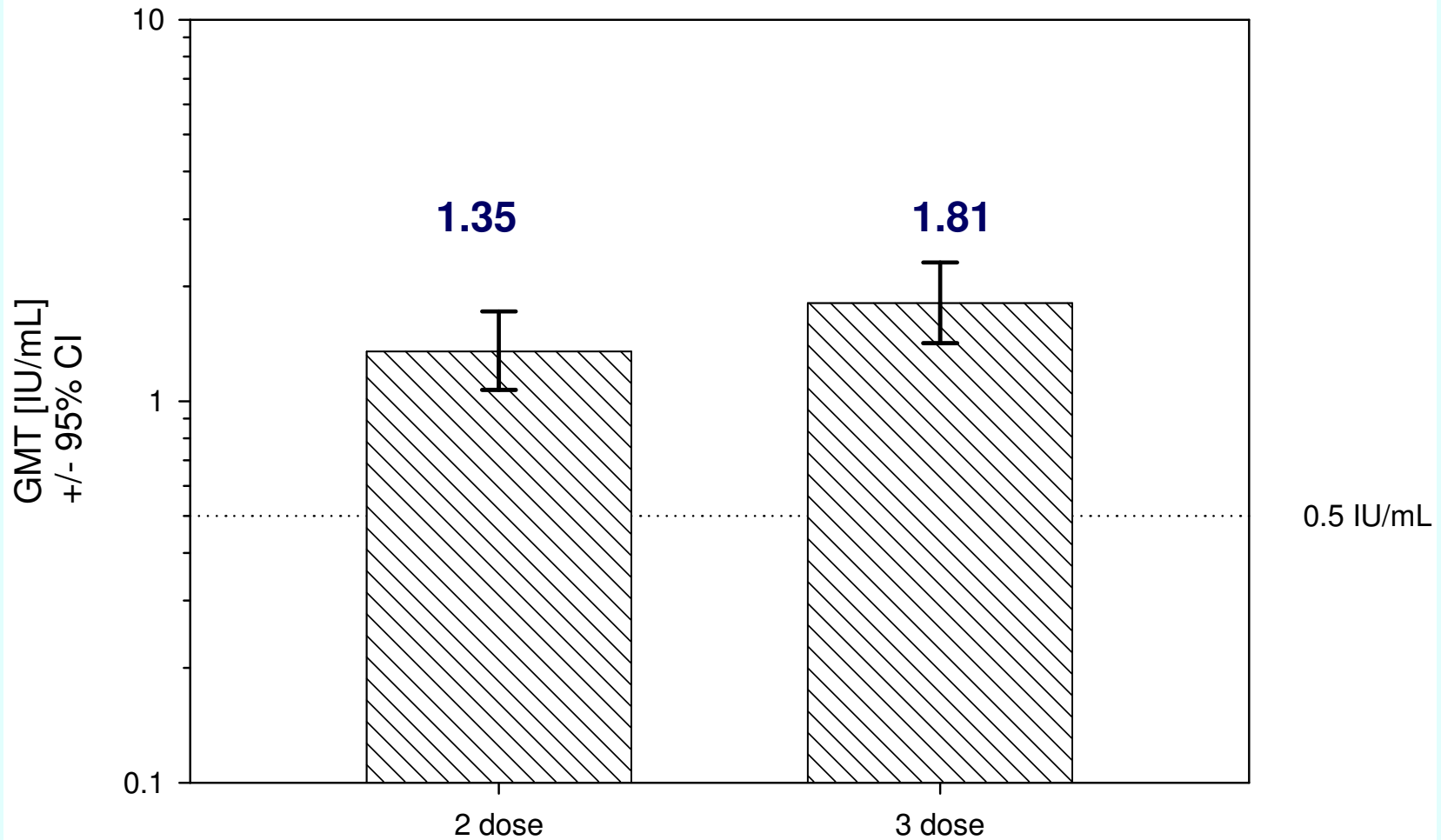
- 150 children aged 5-9 yrs in Kananga, Leyte were given pre-exp vaccination following 2 schedules:
 - 2 ID doses – day 0 and 28
 - 3 ID doses – day 0, 7 and 28
- 79 F, 71 M; mean age - 7.2 yrs



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RVNA (RFFIT) on Day 49 (per-protocol)



Subjects with adequate titers (> 0.5 iu/ml) on day 14

2 ID doses

63/73
86%

3 ID doses

69/70
99%

10 subjects from 2-dose group
& 1 subject from 3-dose group
not reaching adequate titers were
given an additional vaccine dose

3-dose ID regimen better than 2-dose ID regimen for pre-exposure immunization



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Immunogenicity

- The WHO approved pre-exposure prophylaxis schedules have been shown to provide reliable, long-lasting Ab titers that result in an accelerated Ab response **if 2 booster doses are administered after simulated exposure**
- No evidence of interference in development of Ab to diphtheria, polio and rabies when PVRV is given with DPT-IPV in EPI program



Safety

- **Local reactions at the injection site**
 - Induration, pruritus > erythema, pain
 - Mild and transient
- **Systemic reactions – uncommon (<5%)**
 - Headache, malaise, fever, muscle and joint pains
 - Mild and transient
 - Severe allergic reactions rare



Cost effectiveness

- Deaths due to rabies are responsible for 1.74M DALYs lost each year; additional 0.04 M DALYs lost through morbidity and mortality from NTVs
- DALY - disability adjusted life yr
 - Direct DALY score – derived from mortality due to the disease
 - Indirect DALY score – morbidity and mortality from side effects of NTV
- Cost burden: \$ 580 million
 - Total Asia: \$ 560 M (96.5%)
 - Total Africa: \$ 20 M (3.5%)



Cost effectiveness

- Total predicted annual human rabies deaths averted with current level of human PEP: 280,000
- Costs due to rabies
 - Direct (medical) human costs from PEP (vaccine, RIG, cost of administration, materials, salaries)
 - Indirect (patient) costs from PEP (transportation costs, loss of income)
 - Costs to control rabies among dogs
 - Livestock losses
 - Surveillance costs



Cost effectiveness

- The average cost of PEP for a 30 kg child with severe exposure is at least P6265 using the ERIG and IM regimen of rabies vaccine. The cost escalates to P14, 845 if HRIG is used
- Of the 136,429 bite victims in 2006
 - only 63.5 % received vaccine
 - only 28 % of the severe exposures were given RIG



Cost effectiveness

- Chulasugandha P, Khawplod P, Havanond P, Wilde, H. *Cost comparison of rabies pre-exposure vaccination with post-exposure treatment in Thai children. Vaccine* 2006. 24 (9): 1478-1482
 - Results - costs of both strategies, PrEP of children or PEP of exposed, become equal when the dog bite incidence is 7-14%; depending on which PEP Tx regimens are used



PIDSP/PPS Recommendation

- **Choice of rabies vaccine, route of administration, age and schedule for primary pre-exposure vaccination in the Philippines should take into consideration the ff:**
 - **Risk for rabies exposure**
 - **Feasibility of integration into the current childhood immunization schedule**
 - **Availability and cost of the vaccines balanced with other public health measures such as control of animal rabies and post-exposure prophylaxis**



PIDSP/PPS Recommendation

- Rabies is a 100% fatal disease that is completely preventable
- Targeted approach
 - Implement pre-exposure rabies vaccination in provinces or regions with the highest rates of animal or human rabies cases
 - Offer pre-exposure prophylaxis as an option to children residing in regions with rabies incidence rate of <3 cases/million pop



Recommended regimens

- **Intramuscular regimen**
 - Recommended for clinics where only 1 or 2 children are seen at any one time
- **Intradermal regimen**
 - Recommended for schools and animal bite treatment centers where a lot of children can be scheduled for vaccination at the same time



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**

Guidelines

- **Vaccine is administered into the upper arm (deltoid region) of adults and into the anterolateral thigh region of young children**
- **Vaccine should never be administered into the gluteal region as absorption is unpredictable.**
- **Reconstituted vaccine vials should be kept in the refrigerator (2-8⁰C) and consumed within 6-8 hrs**



Guidelines

- **Booster doses are not mandatory but may be given every 3 years depending on continuing risk of exposure**
- **Any exposure**, regardless of severity, after completion of the primary immunization should be given rabies vaccine as follows:

Interval from last dose	Booster
0-6 months	1 booster dose
> 6 months to 3 years	2 booster doses (days 0 and 3)
> 3 years	Full course of vaccine without RIG





**National Rabies
Prevention and
Control
Program,
Philippines**

**GOAL:
To eliminate
human rabies and
declare the
Philippines RABIES
FREE by 2020**



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Pre-exposure prophylaxis

- **Philippines is the first country to implement wide scale pre-exposure vaccination among children**
- **Vaccinate 50,000 school children/year in high risk areas**
- **High risk areas: regions with highest incidence of human rabies cases**
 - **Region 2 (8.65/M pop)**
 - **Region 12 (5.2/M pop)**
 - **Region 8 (4.86/M pop)**
 - **Region 5 (4.18/M pop)**
 - **CAR (3.91/M pop)**



Pre-exposure prophylaxis

- **Strategy**
 - **Immunize all children grades 1-6 initially**
 - **Immunize only grade 1 school entrants in succeeding years**
- **In regions where rabies control measures on dogs are not effective and there is a high incidence of canine rabies, pre-exposure vaccination may be considered as a temporary strategy**
 - **It must never detract from the efforts to control rabies in the canine population**

