Introduction of rabies vaccines into immunization programs

Deborah J Briggs

Global Alliance for Rabies Control

ADVAC
Mérieux Foundation
Annecy

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Regions of highest risk

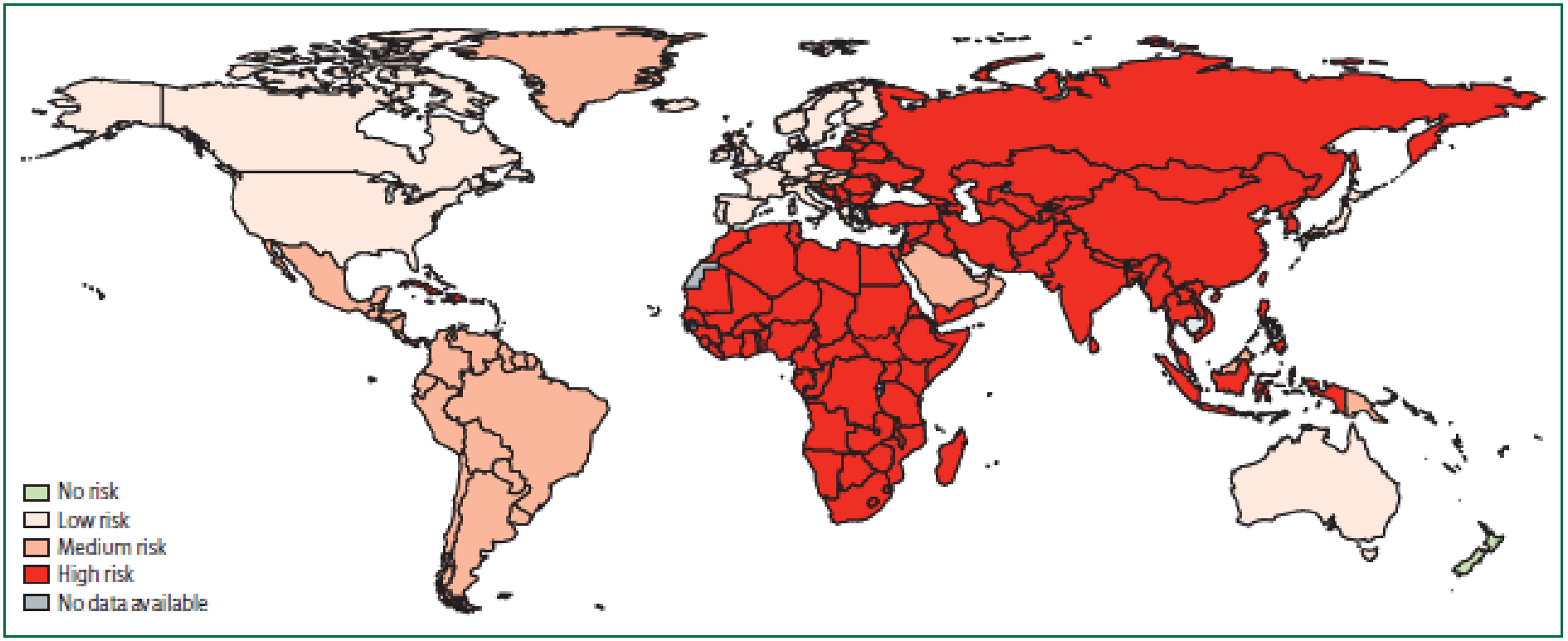


Figure 1: **WHO rabies risk map**

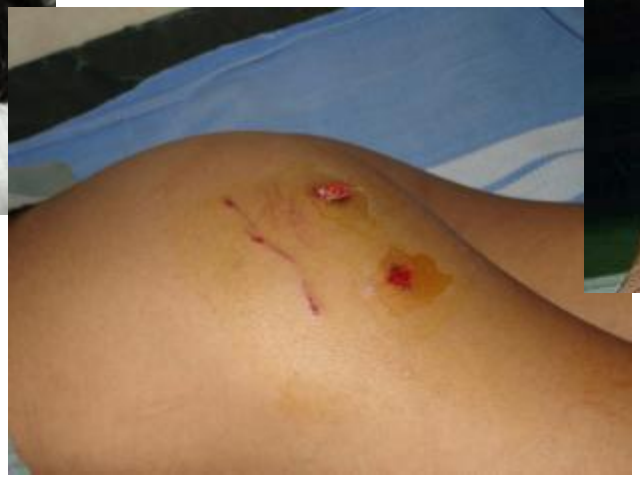
Data from WHO. Most of the cases of human rabies occur in Africa and Asia. Attempts to accurately map the distribution of rabies risk or incidence show the absence of quantitative data and the irrelevance of political boundaries in the control of a disease with animal reservoirs. In low-risk areas, pre-exposure immunisation is recommended for individuals who will come into contacts with bats. In medium risk areas, pre-exposure immunisation is recommended for individuals who will come into contact with bats and other wildlife. In high-risk areas, pre-exposure immunisation is recommended for individuals who will come into contact with domestic animals such as dogs, and other rabies vectors.

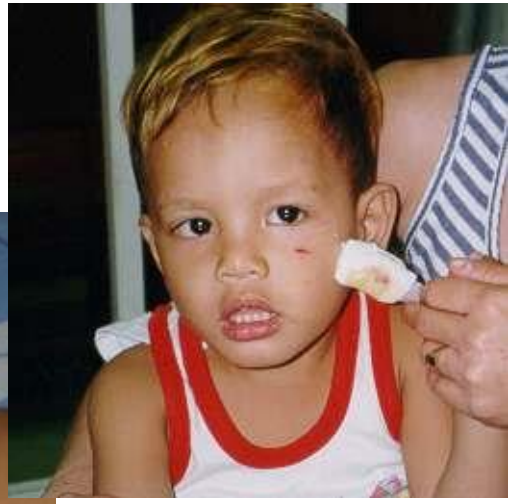
Current situation

- **Fatal viral disease > 95% caused by dog bites - 100% preventable by vaccination**
- **Rabies vaccines can be administered after exposure (PEP) or as preventative vaccination (PreP)**
- **22 million people exposed annually – mostly children**
- **One child dies of rabies every ~ 10 minutes**
- **No or limited access to PEP in many remote rural regions where vampire bat and canine rabies is endemic**

Dog Bite Facts

Photos: KIMS, Bangalore

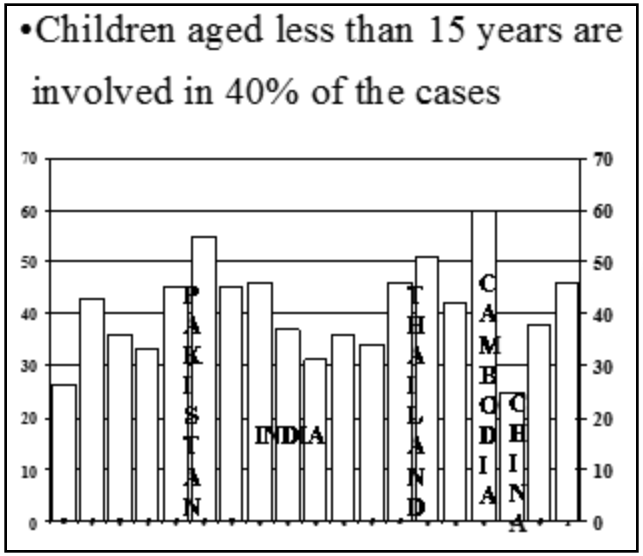


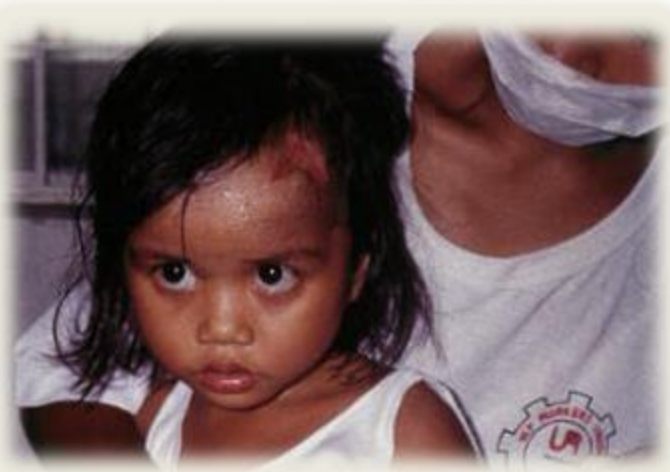


Photos: Dr Steven Scholand

More than half of all children will be victims of a dog bite by the time they reach age 12

Dog Bite Facts





Every dog bite in a rabies-endemic country must be considered a potential exposure

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The Telegraph

Vampire bats kill five children in Peru

At least five children living in Peru's northern Amazon jungle region h
being bitten by rabid vampire bats, the health ministry said on Wedn

Rabid vampire bats have attacked more than 500 people in Peru's Amazon, killing five children Photo: PHOTOLIBRARY

12:42AM BST 23 Sep 2010

At least five children living in **Peru**'s northern Amazon jungle region have died after being bitten by rabid vampire bats, the health ministry said on

At least five children living in **Peru**'s northern Amazon jungle region have died after being bitten by rabid vampire bats, the health ministry said on Wednesday.

The victims, all aged between five and 10, were members of the Awajun and Wampis communities living in the province of Condorcanqui, 620 miles north of Lima on the border with Ecuador.

Fernando Borjas, a medical doctor with the health directorate in the regional capital Chachapoyas, said that the rabies outbreak has been going on for several months.

Health authorities have sent teams with vaccines to the remote jungle villages, but after a 15 hour river trip they often arrive too late.

"I cannot discount the death toll mounting, because unfortunately we cannot get them the vaccines quickly enough because the communities are so remote," Mr Borjas said.

Am. J. Trop. Med. Hyg., 87(2), 2012, pp. 206–215
doi:10.4269/ajtmh.2012.11-0689

Evidence of Rabies Virus Exposure among Humans in the Peruvian Amazon

Amy T. Gilbert,*† Brett W. Petersen,† Sergio Recuenco, Michael Niezgoda, Jorge Gómez, V. Alberto Laguna-Torres, and Charles Rupprecht

National Center for Emerging and Zoonotic Infectious Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia; Dirección General de Epidemiología, Ministerio de Salud, Lima, Perú; Epidemic Intelligence Service, Centers for Disease Control and Prevention, Atlanta, Georgia; Virology Department, US Naval Medical Research Unit 6, Lima, Perú

Abstract. In May of 2010, two communities (Truenococha and Santa Marta) reported to be at risk of vampire bat depredation were surveyed in the Province Datem del Marañón in the Loreto Department of Perú. Risk factors for bat exposure included age less than or equal to 25 years and owning animals that had been bitten by bats. Rabies virus neutralizing antibodies (rVNAs) were detected in 11% (7 of 63) of human sera tested. Rabies virus ribonucleoprotein (RNP) immunoglobulin G (IgG) antibodies were detected in the sera of three individuals, two of whom were also seropositive for rVNA. Rabies virus RNP IgM antibodies were detected in one respondent with no evidence of rVNA or RNP IgG antibodies. Because one respondent with positive rVNA results reported prior vaccination and 86% (six of seven) of rVNA-positive respondents reported being bitten by bats, these data suggest nonfatal exposure of persons to rabies virus, which is likely associated with vampire bat depredation.

Gilbert et al. Am J Med Hyg. 2012

TABLE 3

Indication of bat exposure and prior pre- or post-exposure prophylaxis history among seropositive survey respondents

Gender (age in years)	Location	RFFIT (IU/mL)	IFA		Bat exposure*	Bat bite	PreEP/PEP
			IgG	IgM			
Male (48)	Truenococha	0.4	1:128	–	Yes	No	No
Male (54)	Truenococha	ct	1:128	–	Yes	Yes	No
Male (34)	Santa Marta	0.6	–	–	Yes	Yes	No
Male (40)	Santa Marta	< 0.05	–	1:8	Yes	No	nd
Female (49)	Santa Marta	0.4	–	–	Yes	Yes	nd
Male (39)	Santa Marta	2.8	–	–	Yes	Yes	No
Male (49)	Santa Marta	0.4	–	–	Yes	Yes	No
Male (47)	Santa Marta	0.6	–	–	Yes	Yes	No
Female (27)	Santa Marta	0.1	1:8	–	Yes	Yes	PEP

*Bat exposure defined as a bite, scratch, or direct contact with unprotected skin.
ct = cytotoxic; IFA = indirect fluorescent antibody; IU = international unit; Ig = immunoglobulin; nd = not determined; PEP = post-exposure prophylaxis; PreEP = pre-exposure prophylaxis; RFFIT = rapid fluorescent focus inhibition test.

63 sera obtained from respondents (age 2 – 62) mean age 29 years;

11% (7 out of 63) showed rVNA (titer 0.1 – 2.8 IU/mL)

Gilbert et al. Am J Med Hyg. 2012

Rabies is under-reported, misdiagnosed

DISPATCHES

Rabies Encephalitis in Malaria-Endemic Area, Malawi, Africa

Macpherson Mallewa,*† Anthony R. Fooks,‡ Daniel Banda,† Patrick Chikungwa,§ Limangeni Mankhambo,† Elizabeth Molyneux,† Malcolm E. Molyneux,† and Tom Solomon*

In a malaria-endemic area of Africa, rabies was an important cause of fatal central nervous system infection, responsible for 14 (10.5%) of 133 cases. Four patients had unusual clinical manifestations, and rabies was only diagnosed postmortem. Three (11.5%) of 26 fatal cases originally attributed to cerebral malaria were due to rabies.

Emerging Infectious Diseases • www.cdc.gov/eid • Vol. 13, No. 1, January 2007

10.5 % of children originally diagnosed with cerebral malaria in Malawi died of rabies

Rabies dilemma

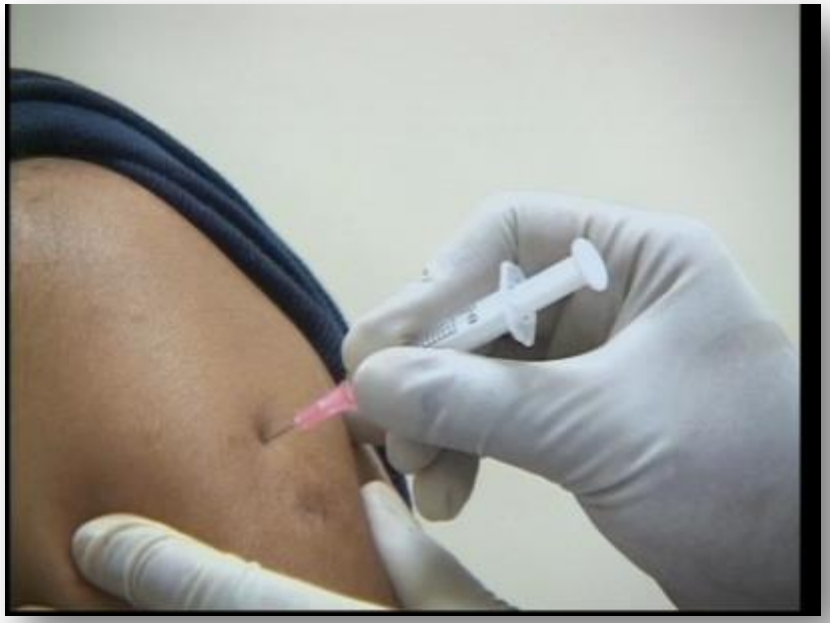
Re-evaluation of global burden
Partners for Rabies Prevention

- 74,000 deaths per year
  - >90% in Africa, Asia
- 2.3 mio DALYs
- Burden 5.5 billion US$
  - 37% due to PEP

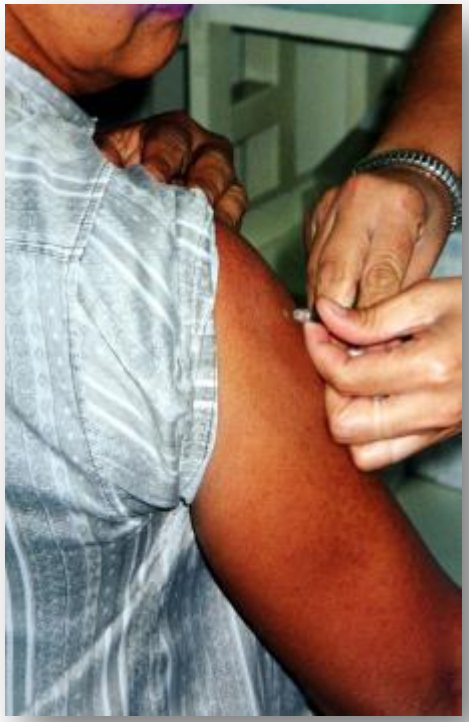
Rag pickers/municipal corporation workers waiting for preventive rabies vaccination in Shimla, India

Global Study data by Hampson and PRP 2014

WHO Prequalified vaccines can be administered IM or ID for PreP and PEP



Intramuscular regimen



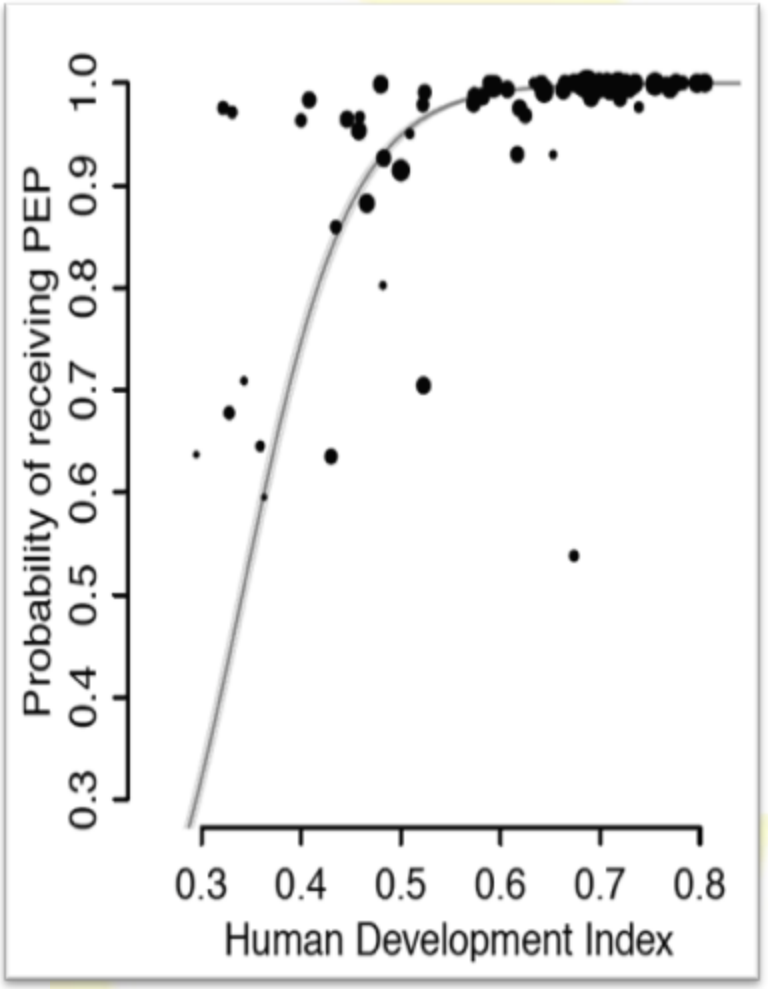
Intradermal regimen

Rabies vaccine regimens - WHO

Type	Route	Previously Vaccinated?	Rabies Ig required?	Injection days	Number of vials
PEP Essen	IM	NO	YES	0,3,7,14,28	5
PEP Zagreb	IM	NO	YES	0,7,21	4
PEP Thai Red Cross	ID	NO	YES	0,3,7,14,28	1 - 2
	IM ID	YES YES	NO NO	0, 3 0,3 or 0 (X4)	< 1 < 1 - 1
PreP	IM ID	NO	NO	3 < 1	3 < 1

Why do patients still die?

- PEP protects after exposure if the patient receives WHO recommended medical attention
  - IM and ID
- Lack of access, knowledge, affordability (poverty)
- ***PreP in specific circumstances can reduce death and IMPROVE ACCESS***



K Hampson Global Burden study, 2014

PreP Studies in Children

- Many published clinical trials available
- Successful long term immunity proven:
  - in association with DPT-IPV in infants – five year follow up proved successful booster response
  - in association with JE vaccine in toddlers
  - in school age children
  - Using both IM and ID administration

TRANSACTIONS OF THE ROYAL SOCIETY OF TROPICAL MEDICINE AND HYGIENE (1999) 93, 208–213

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. Hoa[2], Nguyen V. Gioi[2], Le Than Tho[2], Nguyen C. Vien[2], Nicolas Rouyrre[1] and Remi Forrat[1] [1]*Pasteur Mérieux Connaught, Lyon, France;* [2]*Pédiatrie Developpement et Santé, Ho Chi Minh City, Viet Nam*

PreP and DTP-IPV
235 subjects
PVRV administered IM (2 and 4 mo) and ID (2,3, and 4 mo)
All reported to have seroconverted

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Journal of Tropical Pediatrics Advance Access published November 29, 2007

Pre-exposure Purified Vero Cell Rabies Vaccine and Concomitant Routine Childhood Vaccinations: 5-year Post-vaccination Follow-up Study of an Infant Cohort in Vietnam

by Jean Lang,[a] Emmanuel Feroldi,[a] *and* Nguyen Cong Vien[b]
[a]*Sanofi Pasteur, Marcy L'etoile, France*
[b]*Center of Pediatrics, Development and Health, Children's Hospital No. 2, Ho Chi Minh City, Vietnam*

WORLD RABIES DAY SEPTEMBER 28

Transactions of the Royal Society of Tropical Medicine and Hygiene (2008) 102, 294–296

available at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevierhealth.com/journals/trst

SHORT COMMUNICATION

Long-term anti-rabies antibody persistence following intramuscular or low-dose intradermal vaccination of young Vietnamese children

Nguyen Cong Vien[a], Emmanuel Feroldi[b], Jean Lang[b,*]

Summary Vietnamese children received purified Vero cell rabies vaccine 1 year after a primary series (Y0) and again 5 years later (Y5), either as intramuscular or 1/5th dose intradermal injections concomitant with diphtheria, tetanus, pertussis and oral poliomyelitis vaccines. Antibody levels were assayed annually for 5 years. All subjects in both groups had anti-rabies antibody titres considered protective after the Y0 booster. Rabies seroprotection rates and geometric mean titres gradually decreased similarly in both groups. Seroprotection after the Y5 booster was 100% in both groups. Satisfactory immunogenicity, long-term antibody persistence and an anamnestic response were conferred by both routes, greatly simplifying any future post-exposure prophylaxis.

Vien et al. 2008

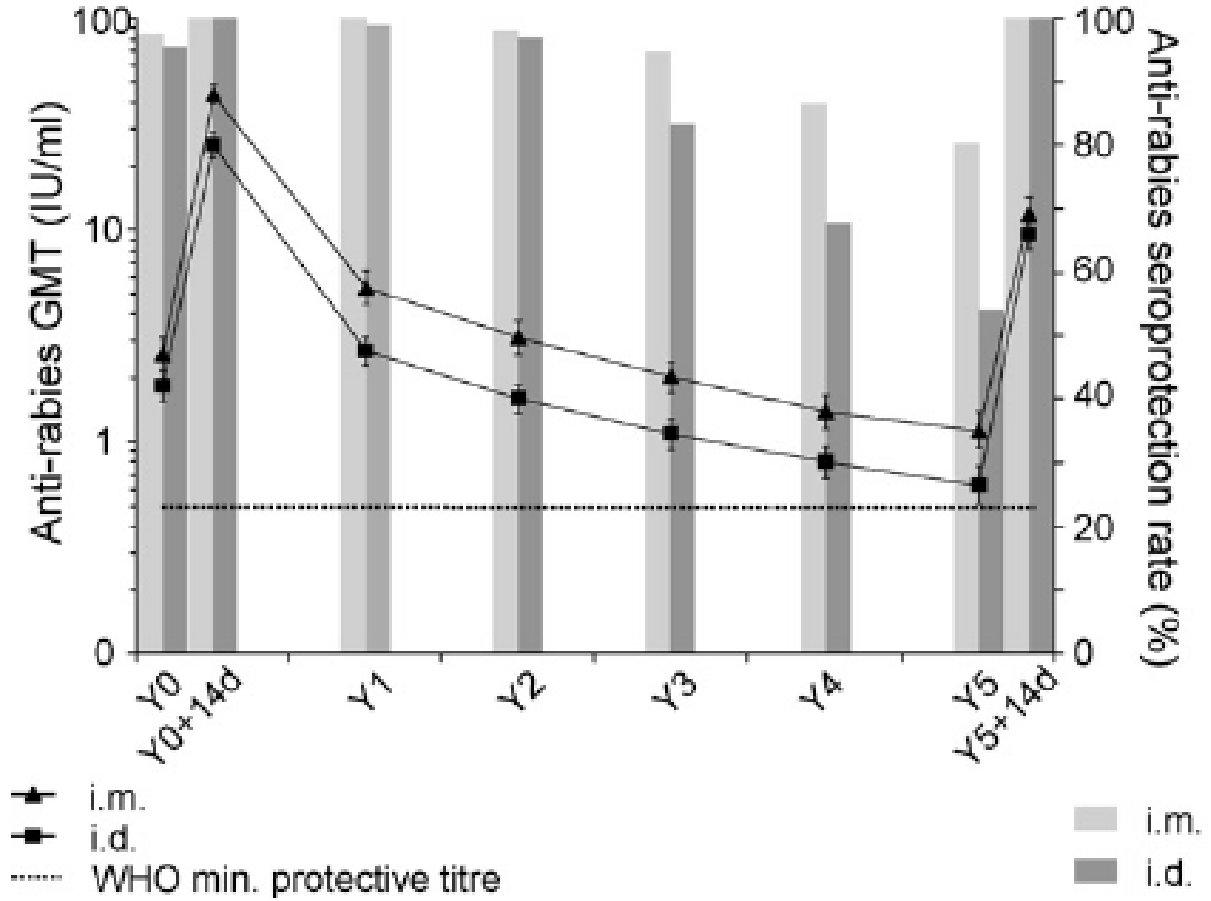


Figure 1 Anti-rabies antibody titre [geometric mean titre (GMT) and 95% CI, log-scale representation] kinetics and sero-protection (% subjects titre ≥0.5 IU/ml) following pre-exposure purified Vero cell rabies vaccine administered i.m. or i.d.

Vien et al. 2008

PEP and PreP in Children
List of publications on PCECV

Table 1. Clinical trials with Novartis Vaccines' PCECV in children

Study	Publication/Year	N[a,b]	Route	Age[c]	Results
1	Lumbiganon et al. 1989[24]	24 (24)	IM	2–15 y	All children had VNA concentrations > 0.5 IU/mL on day 14, PCECV well tolerated
2	Pengsaa et al. 2009[25]	177 (177)	IM/ID	12–18 mo	IM administration resulted in 3- to 5-fold higher titers than ID; After 1 y all VNA concentrations were > 0.5 IU/mL in IM groups; all subjects had anamnestic responses to booster doses. Both IM and the 3-dose ID regimens demonstrated long-lasting immunogenicity, with persistence of immunological memory. PCECV was well tolerated. PCECV and JEV administered concomitantly were immunogenic and safe and did not influence each other.
3	Kamoltham et al. 2007,[26] Kamoltham et al. 2011[27]	703 (73[d]/147[e]) 703 (703)	ID	4–8 y	Robust immune responses were detected in all children by day 49. Up to 5 y after primary vaccination, anamnestic immune responses occurred after two ID booster doses. No serious adverse reactions were seen.
4	Shanbag et al. 2008[28]	115 (115)	IM	3–12 y	All subjects developed adequate VNA concentrations by day 49; PCECV was well tolerated, regardless of the volume used for reconstitution
			Additional supporting studies		
5	Sampath et al. 2005[30]	45 (39)	IM (PEP)	8 mo to 16 y	Adequate immune responses by day 14 were detected in all subjects, regardless of the grade of malnutrition.
6	Ogutu et al. 2009[31]	191 (-)	IM	12–47 mo	Safety assessment only, PCECV was well tolerated.

[a]Subjects receiving PCECV; additional study arms with comparator vaccine not taken into consideration. [b]Actually enrolled and available for safety analysis, per-protocol immunogenicity analysis in parentheses. [c]At the time when the primary vaccination series was administered. [d]Available for immunogenicity after primary vaccination. [e]Available for immunogenicity after booster vaccination.

Malerczyk and Bender; Hum Vacc & Immunotherap 2013

CARe

CHILDREN AGAINST RABIES

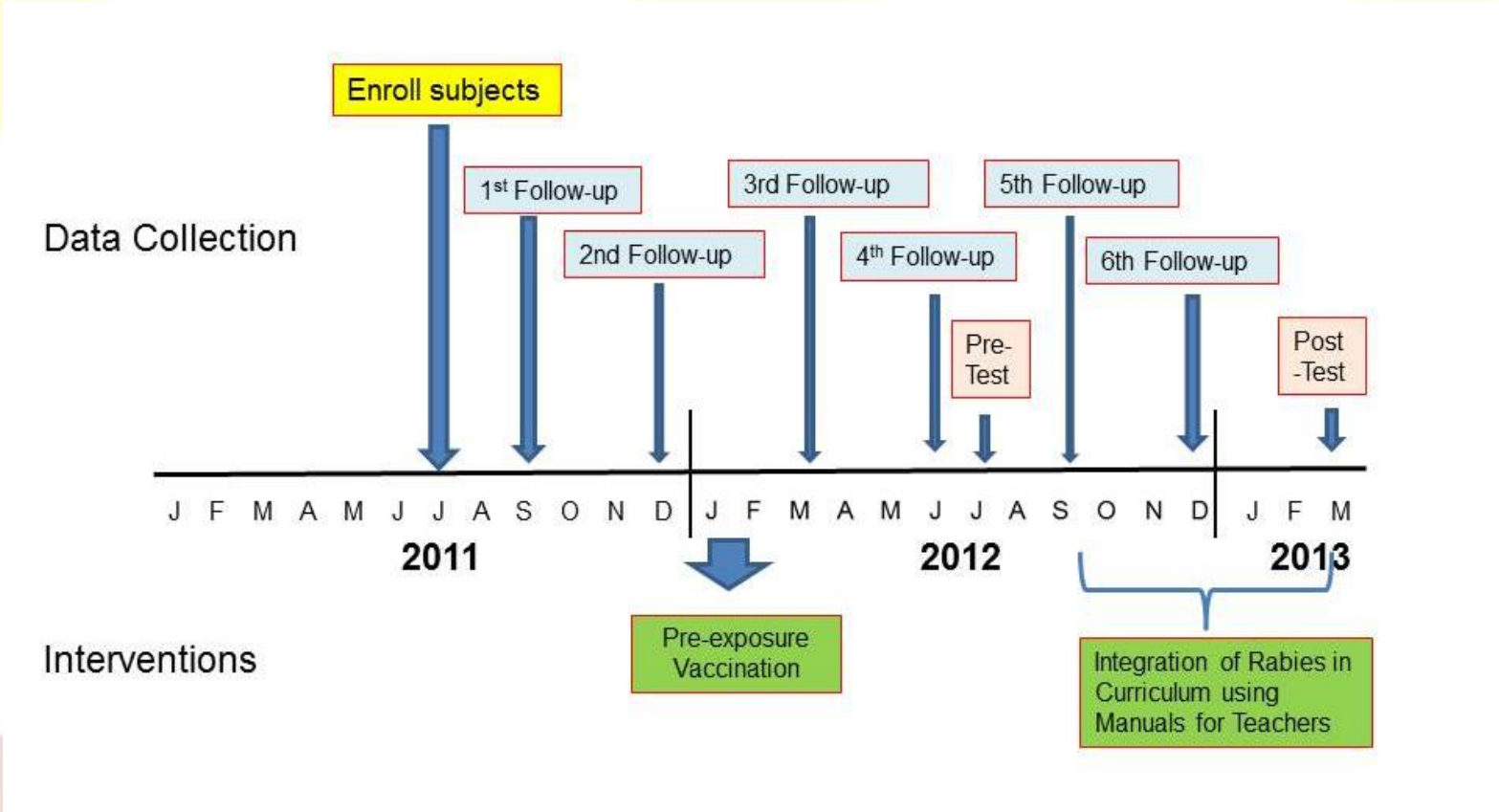
Evaluation of a prevention campaign on rabies exposure burden among school age children living in El Nido, Philippines

Interventions in One Rural Municipality

- Pre-exposure vaccination of 4600 children (**84%** of kids 5-14 yrs old) (3 doses within one month) – given on Jan-Feb 2012

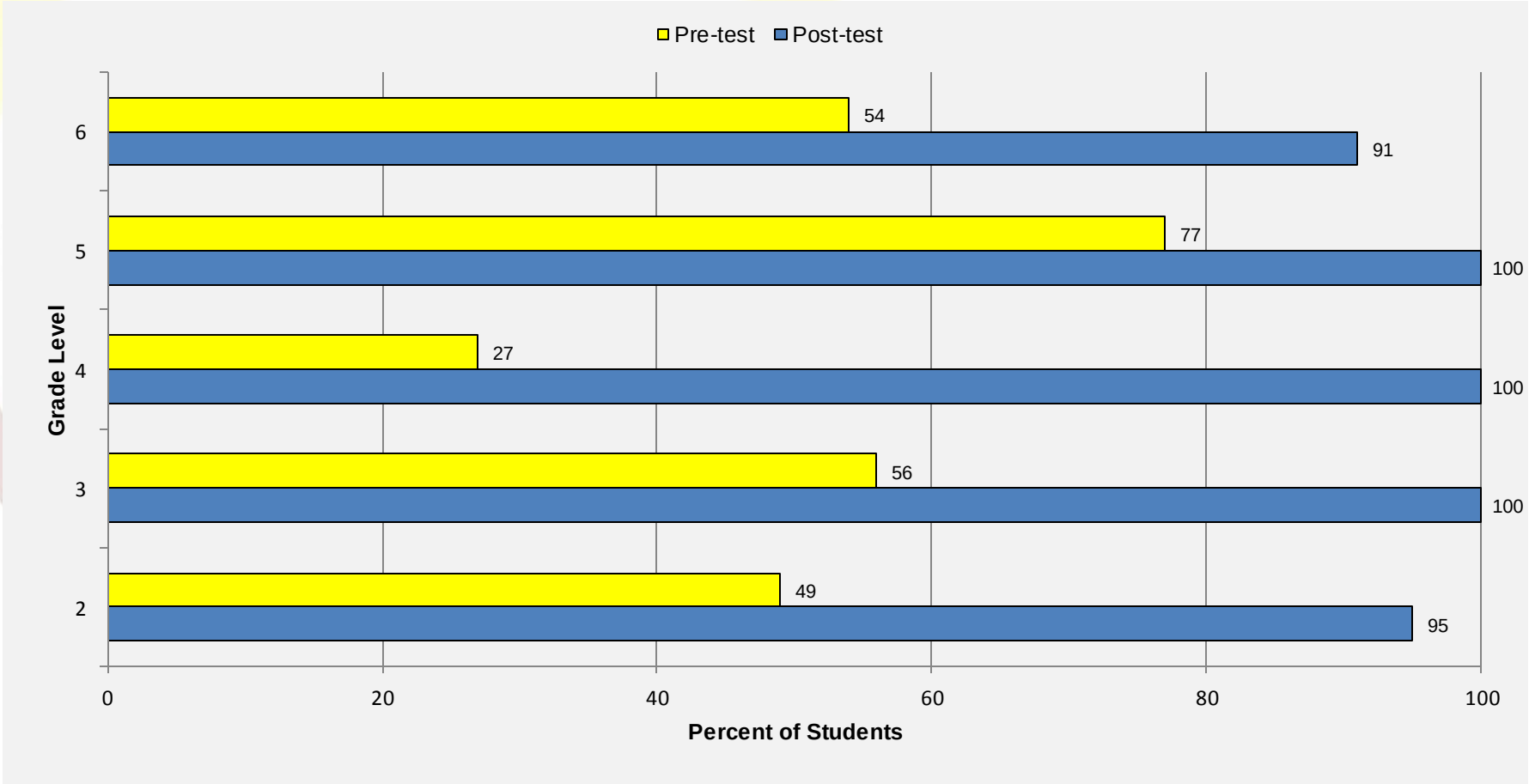
- Integration of rabies education in school curriculum

Rabies Education & PreP
El Nido Philippines



Child education intervention

Percentages of students who knew about Rabies based on pre and post-tests of students in El Nido Elementary Schools, School Year 2012-13



Opportunities & Challenges

- Rabies vaccines are highly efficacious
- *Change of strategy* to use PreP rather than PEP when more appropriate
- ***Target specific populations*** rather than global coverage for PreP – reduce cost per life saved
  - Efficacy is high in all age groups: Age for roll out of PreP may vary according to risk & access
- Incorporating PreP into other vaccine regimens when & where appropriate – highly immunogenic with childhood vaccines – can help reduce delivery cost

Future Directions

- Increase utilization of PreP in high risk regions with limited to no access to PEP
- Move toward ID administration to reduce cost
- Improve educational awareness in association with vaccine programs
- Ultimate goal is to eliminate rabies at the major source of infection – ie canine population *but first line of defense is to save human lives*

Working with Communities for Rabies Prevention