



Pre-Exposure Prophylaxis of Rabies in Humans

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Rabies Epidemiology: some important facts

- An estimated **15 million** people receive **Post-Exposure Prophylaxis** each year after being exposed to rabies suspected animals
- On average **30-60% of rabies cases** in human occur in **children** residing in enzootic areas
- **Bites to travelers** by potentially rabid animals are relatively **frequent**: estimated incidence is **0.4% per month** of stay, according to a meta-analysis of **≈1,270,000** travelers

Gautret et al. Emerging Infectious Disease. 2015;21(4):569-577.

WHO Expert Consultation on Rabies second report, 18-20 September 2012. TRS 982 WHO Geneva 2013.

Gibbons RV. Rabies and related diseases. Encyclopedia of life sciences. Chichester: John Wiley & Sons, Ltd.; 2001.

Sanofi Pasteur internal data



RABIES Immunization

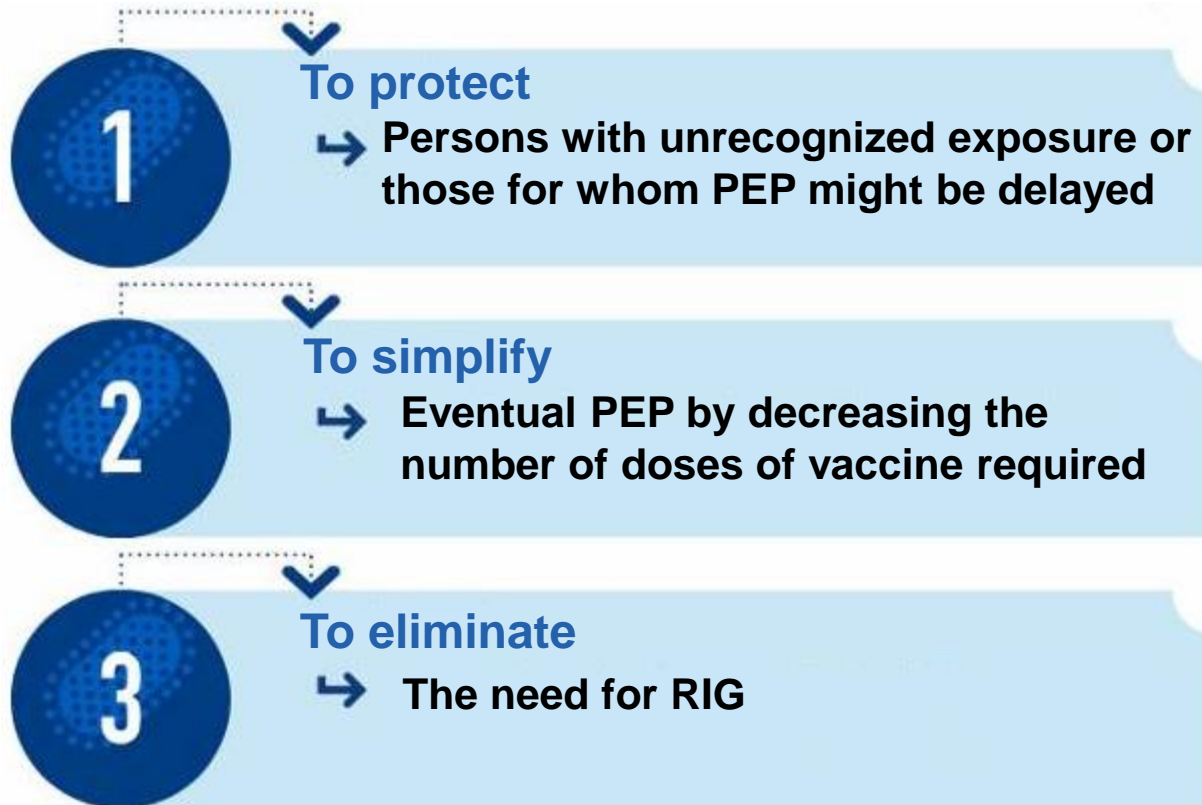


Pre-Exposure Prophylaxis (PrEP)

According to WHO, PrEP is recommended for anyone at increased risk of exposure to rabies virus

WHO Expert Consultation on Rabies second report, 18-20 September 2012. TRS 982 WHO Geneva 2013.

PrEP: Rationale





PrEP: Target populations (1/3)

SUBJECTS AT PERMANENT RISK MUST BE VACCINATED

- ▶ Diagnostic, research and production, laboratory staff

SUBJECTS AT FREQUENT RISK SHOULD BE VACCINATED

- ▶ Nurses, medical staff, animal handlers and veterinarians



PrEP: Target populations (2/3)



IN PARTICULAR CHILDREN SHOULD BE VACCINATED

▶ **Children are at higher risk of animal bites**

- ┌ Their small size makes them less intimidating to animals
- ┌ They fail to recognize and avoid threatening behavior
- ┌ They are less able to shelter themselves or escape when attacked
- ┌ Their stature make them especially vulnerable to severe facial and head bites, which carry the highest risk of disease

▶ **Children have a faster development of rabies disease than do adults**

▶ **Unapparent, unrecognized or unreported exposure increases the risk for children to be untreated**

PrEP in school-age children: The Philippines experience

Global Alliance for Rabies Control: “**CARe**” (**Children Against Rabies**) study: education program on rabies among school-age children in El Nido, Philippines

- ▶ Primary objective: To estimate the incidence of contact with rabies suspected animals in school-age children in the Philippines (grades 1-5) using active surveillance and compare this to estimates from the existing passive surveillance system (collected by ABTC)

In parallel of this study, a **vaccination campaign** conducted by the Department of Health in the same region:

- ▶ 3 ID doses at days 0, 7, and 28

A total of **6,763 children** were enrolled in **27 public schools** from June 2001 to December 2012

- 142 (3.2%) children had a history of animal bite
- Introduction of rabies education in the curriculum all along the year by teachers



HE assessment: the costs of PrEP could be recouped in 5 years

PrEP: Target populations (3/3)

TRAVELERS ARE PARTICULARLY LIKELY TO BE EXPOSED

▶ Travelers are at higher risk of rabies exposure

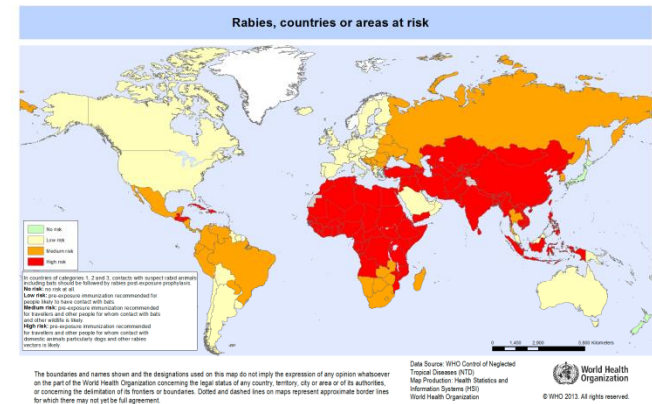
- Outdoor activities such as camping, bicycling, hiking etc. increase the risk for travelers to be exposed to rabies, even if the trip is brief

▶ Travelers have an increase risk of developing rabies

- Risk of delay in rabies PEP
- Risk of no access to medical services and PEP abroad
- Risk of unapparent or unrecognized exposure to rabies virus

▶ WHO recommends PrEP:

- LOW** risk areas: For people likely to get in contact with bats
- MEDIUM** risk areas: Travelers/people likely to get in contact with bats and other wildlife
- HIGH** risk areas: Travelers/people likely to get in contact with domestic animals and other rabies vectors



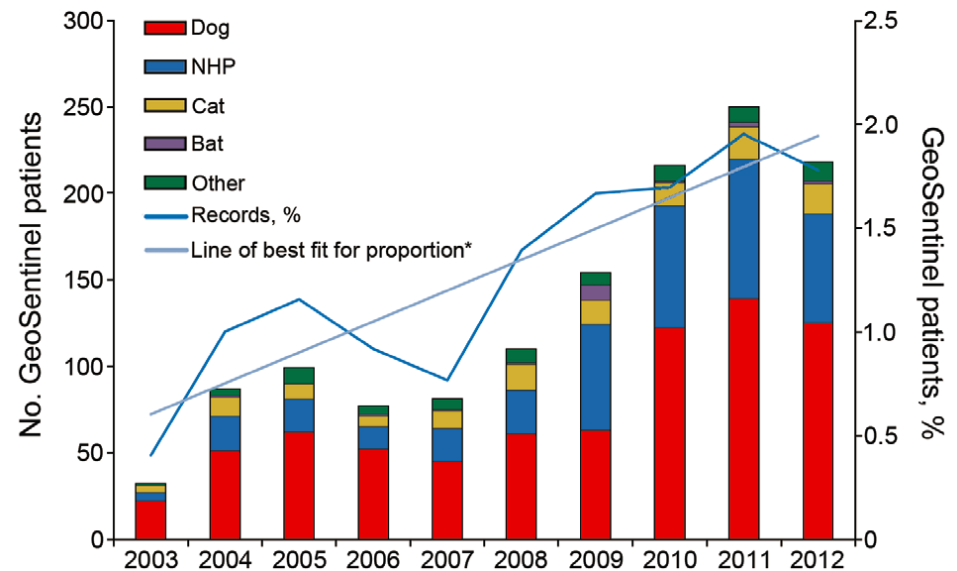
WHO Expert Consultation on Rabies second report, 18-20 September 2012. TRS 982 WHO Geneva 2013.
WHO. International travel and health. Geneva, 2014

PrEP: Providing appropriate information for travelers (1/2)

Animal-associated exposure to rabies among travelers, 1997–2012 [Gautret, 2015]

A comprehensive survey (2,697 patients, 16 years, 45 sites)

- The short median duration of travel (2 weeks) among travelers consulting for PEP corroborates the WHO recommendation that a **travelers' assessment for risk of an animal bite should not be influenced by the duration of travel** [WHO, 2013].
- Results, however, are not consistent with the current CDC recommendations that **PrEP may be recommended based on ... duration of stay** [Rupprecht, 2014], a position that is shared by many countries.



Number of patients requiring PEP and line of best fit for proportion of all GeoSentinel records accounted by animal-related exposure requiring PEP [Gautret, 2015]

PrEP in travelers need to be reinforced

Gautret et al. Emlerging Infectious Disease. 2015;21(4):569-577.

WHO Expert Consultation on Rabies second report, 18-20 September 2012. TRS 982 WHO Geneva 2013.

Rupprecht CE, Shlim SD. Infectious diseases related to travel – rabies. In: CDC health information for international travel 2014.

<http://wwwnc.cdc.gov/travel/yellowbook/2014/chapter-3-infectious-diseases-related-to-travel/rabies>

PrEP: Providing appropriate information for travelers (2/2)

The outbreak of rabies in Bali

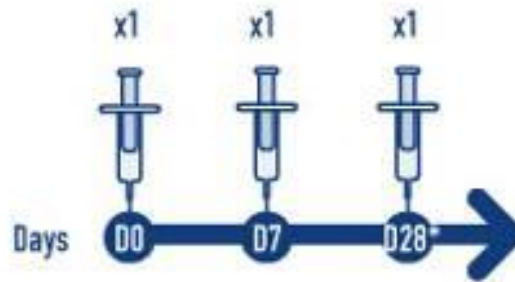
- Bali authorities estimate around **85 dog bites per day island-wide** (600,000 dogs in the island)
- Since November 2008 a total of **31,000 dog bite injuries** have occurred with **28,000 people** being given PEP
- **120+ confirmed cases of human rabies**
- Most rabies cases have been confirmed near **popular tourist destinations**
 - ▶ CDC advises travelers to take precaution on the entire island



CDC <http://wwwnc.cdc.gov/travel/content/outbreak-notice/rabies-bali-indonesia2008.aspx>

PrEP: vaccination schedule

Primary course:



▶ IM route

- ┌ In the deltoid muscle in adults and children
- ┌ In anterolateral part of the thigh in infants and toddlers

▶ Alternatively ID route (0.1 mL)

- ┌ In countries where ID route for vaccine administration is approved by Health Authorities
- ┌ For vaccines that are recommended by WHO for intradermal use

* D28 injection may also be given at D21

WHO Expert Consultation on Rabies second report, 18-20 September 2012. TRS 982 WHO Geneva 2013.

PrEP: vaccination schedule

- Booster: WHO and CDC USA recommendations on the booster dose of rabies vaccine depend on the risk category of exposure**

| Risk category | Typical populations | Pre-exposure recommendations |
|---------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Continuous | <ul style="list-style-type: none"> ▪ Rabies research laboratory worker ▪ Rabies biologics production workers | <ul style="list-style-type: none"> ▪ Primary course ▪ Serologic testing every 6 months ▪ Booster vaccination if antibody titer is below 0.5 IU/mL |
| Frequent | Rabies diagnostic lab workers, spelunkers, veterinarians and staff, animal-control and wildlife workers in rabies-enzootic areas | <ul style="list-style-type: none"> ▪ Primary course ▪ Serologic testing every 2 years ▪ Booster vaccination if antibody titer is below 0.5 IU/mL |
| Infrequent | <ul style="list-style-type: none"> ▪ Veterinarians and staff, animal-control and wildlife workers in areas with low rabies rates ▪ Veterinary students, travelers visiting areas where rabies is enzootic and immediate access to appropriate medical care including biologics is limited | <ul style="list-style-type: none"> ▪ Primary course ▪ No serologic testing or booster vaccination |

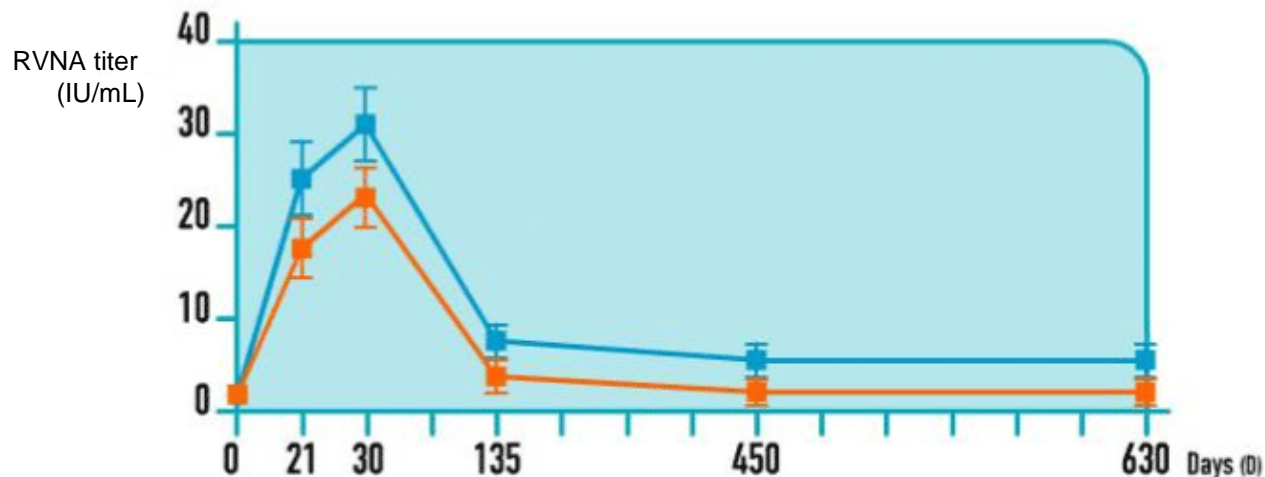
WHO Expert Consultation on Rabies second report, 18-20 September 2012. TRS 982 WHO Geneva 2013.
 Manning SE, Rupprecht CE, Fishbein D, et al. Human rabies prevention--United States, 2008: recommendations of the Advisory Committee on Immunization Practices. MMWR Recomm. Rep. 2008;57(RR-3):1-28.

Pre-Exposure Prophylaxis: Short-term Immunogenicity

- Comparative trials in seronegative adults in: **France** [Ajjan, 1989; Strady, 1998], **Croatia** [Vodopija, 1986], **Kenya** [Kitala, 1990] and **Turkey** [Hacibektasoglu, 1992] (IM doses at D0, D7, D21/D28):

100% of subjects achieved RVNA levels ≥ 0.5 IU/mL at D21/D28 or earlier

[Ajjan, 1989]: 21 months follow-up (no booster): 98% of PVRV and 94% of HDCV vaccinees with RVNA ≥ 0.5 IU/mL

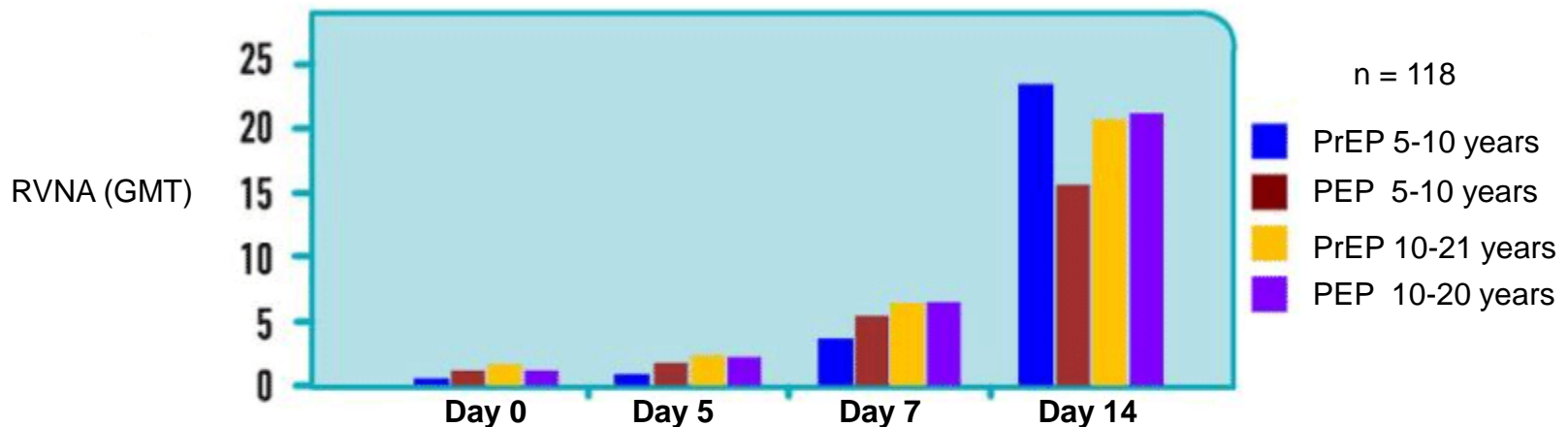


Kinetics of antibody titers following pre-exposure rabies vaccination — HDCV, — PVRV

Adapted from: Ajjan N, Pilet C. Comparative study of the safety and protective value, in pre-exposure use, of rabies vaccine cultivated on human diploid cells (HDCV) and of the new vaccine grown on Vero cells. *Vaccine*. 1989;7(2):125-8.

Pre-Exposure Prophylaxis: Long-term immunogenicity

- Survival of rabies virus-neutralizing antibody in previously vaccinated subjects: long-lasting immunity



GMT of rabies neutralizing antibodies
after PVRV ID boosters on Day 0 and Day 3

Adapted from: Suwansrinon K, Wilde H, Benjavongkulchai M, et al. Survival of neutralizing antibody in previously rabies vaccinated subjects: a prospective study showing long lasting immunity. *Vaccine*. 2006;24(18):3878-80.

PrEP in 'infrequent risk' population: The Thailand experience in health-economics assessment

Cost comparison of rabies PrEP with PEP in Thai children [Chulasugandha, 2006]

- ▶ An analysis model was constructed to compare cost for cohorts of children under 15 years of age who had never received rabies vaccine.
- ▶ The competing strategies were PrEP and PEP regimens

Main results:

- ▶ PrEP has a cost scale which increases with dog bite prevalence
- ▶ When using the least expensive vaccination schedule and no immunoglobulin, PrEP is cost-comparable with PEP when the probability of a dog bite is about 23%
- ▶ If ERIG is used, cost comparability occurred at 7% dog bite prevalence

Direct medical and pharmaceutical costs of PrEP and PEP were equivalent when the annual dog-bite incidence is in the range of 2–30%, depending on PEP regimen used

Chulasugandha P, Khawplod P, Havanond P, Wilde H. Cost comparison of rabies pre-exposure vaccination with post-exposure treatment in Thai children. *Vaccine* 2006;24:1478-82



Positive factors supporting PrEP

- ▶ PrEP simplifies PEP by Rabies Vaccine and RIG savings
- ▶ Significant number of dog bites are not treated. While canine rabies not eradicated, PrEP is a definitive tool to achieve an efficient human rabies prevention
- ▶ Most of dog bites occur in children with severe bites or unnoticed or not reported to parents
- ▶ Main target population: pre-school or school-age children
- ▶ Pediatricians or immunization centers to be the ones giving PrEP to quickly extend the program

Blocking issues could be solved?

- **PrEP awareness and information not developed among parents and healthcare professionals**
 - **Availability of vaccine for PEP is of concern**
 - ▶ Replacement of NTV by CCV impact availability
 - ▶ Public sector not covering all PEP needs today
 - **Question on best strategy to be implemented**
 - ▶ Concern on availability of resources
 - ▶ Logistical constraints to reach most enzootic areas
 - ▶ Target population & schedule: pre-school vs. school-age children
 - ▶ Epidemiology to justify PrEP implementation
 - ▶ Booster policy
 - **Current focus is dog rabies control**
 - ▶ Competing for priority in public health sector
 - **Other healthcare priorities**
 - ▶ Influenza, Meningitis, HIV, TB, others ...
- ➔ • **WRD and Webinar on PrEP?**
 - ➔ • **Worldwide capacities reached about 100 Md, more than 70% served by local producers**
 - **Philippines demonstration project (CARE)**
 - ➔ • **Co-administration with EPI vaccines project (Peru)**
 - **WHO guidelines TRS 982, 2013**
 - ➔ • **Health-economics model established (Thailand)**
 - ➔ • **Assessment of real burden of rabies**



Thank you