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

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.

PrEP: Rationale

1. To protect
   - Persons with unrecognized exposure or those for whom PEP might be delayed

2. To simplify
   - Eventual PEP by decreasing the number of doses of vaccine required

3. To eliminate
   - The need for RIG
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

旅者特别容易接触狂犬病

旅者有更高的狂犬病暴露风险

- 户外活动如露营、骑行、徒步等增加旅者暴露于狂犬病的风险，即使旅行时间短暂

- 旅者有更高的狂犬病发病风险

- 延误狂犬病暴露后预防接种的风险

- 无法获得医疗和暴露后预防措施的风险

- 未察觉或未被识别的狂犬病病毒暴露风险

WHO 推荐 PrEP:

- 低风险区域：与蝙蝠接触的人
- 中风险区域：旅行者/与蝙蝠和其他野生动物接触的人
- 高风险区域：旅行者/与家畜和其他狂犬病媒介接触的人

WHO 专家咨询委员会对狂犬病的第二份报告，2012年9月18-20日。TRS 982 WHO 日内瓦 2013年。

WHO. 国际旅行和健康。日内瓦，2014年

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.

PrEP in travelers need to be reinforced

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 [link](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

PrEP: vaccination schedule

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

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<th>Risk category</th>
<th>Typical populations</th>
<th>Pre-exposure recommendations</th>
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| Continuous    | ▪ Rabies research laboratory worker  
▪ Rabies biologics production workers                                                | ▪ 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 | ▪ Primary course  
▪ Serologic testing every 2 years  
▪ Booster vaccination if antibody titer is below 0.5 IU/mL                  |
| Infrequent    | ▪ 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 | ▪ Primary course  
▪ No serologic testing or booster vaccination                                |

Pre-Exposure Prophylaxis: Short-term Immunogenicity


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

Pre-Exposure Prophylaxis: Long-term immunogenicity

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

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


- 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

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 and 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