RIACON 2009

The Second International Conference of Rabies in ASIA (RIA) Foundation

9-11 September 2009
Horizon Hotel, Hanoi, Viet Nam

CONFERENCE PROCEEDINGS

Edited by
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National Institute of Hygiene and Epidemiology
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GREETING SPEECH

Dr. Nguyen Thi Hong Hanh  
Deputy Director,  
National Institute of Hygiene and Epidemiology  
Co-chair person, RIACON 2009, Vietnam chapter

On behalf of the National Institute of Hygiene and Epidemiology, Ministry of Health, Viet Nam, we sincerely thank the excellent assistance from WHO headquarter in Geneva, Switzerland, Rabies in Asia Foundation in India and all of participating country experts, specialist to attend The 2nd meeting RIACON 2009, VIET NAM CHAPTER held at Horizon Hotel, Hanoi, Viet Nam 9-11 September 2009.

The conference “Rabies in ASIA-Vietnam Chapter 2009” is the 2nd meeting after the first one hold in India two years ago funded by both Sanofi Pasteur and Novartis Vaccines Companies. The conference plays it role as a great opportunity to bring scientists and experts together to simultaneously share information and experience, concurrently update knowledge and search for international collaboration targeted to rabies elimination worldwide. The targets of the 3 day conference enable the interaction of scientists from International organizations, agencies, institutions from both of government and non-governments, ASIA countries to access to the most recent update information of rabies prevention and control methods, vaccine development and technology, technical issues sharing from each countries and sub-continents. The conference also touched the current challenges of rabies on the updated practices in human and animal rabies control, human rabies diagnosis and prevention, sharing the fundamental and implementation research which were useful contributions to improve rabies control, prevention in each ASIA country and the whole region.

Our great honor come to Sanofi Pasteur and Novartis Vaccines Companies for their financial support. Sincerely thank the participation and contribution of all experts, scientists, guests for the successes of the conference.
It is with great pleasure and honour I wish to place on record the meticulous planning, excellent team work and good organizational skills of the staff of National Institute of Hygiene and Epidemiology [NIHE], Hanoi, Vietnam which ensured the successful conduct of the 2nd international conference on rabies viz. RIACON 2009 which was held from September 9 – 11, 2009 at Hanoi Horizon Hotel. The leadership of Drs. Nguyen Tran Hien and Nguyen Thi Hong Hanh and the hard work of Dr. Nguyen Thi Kieu Anh and her colleagues ensured the success of RIACON 2009. In conclusion, the event has set a bench mark for organizers of RIACONS in future.

The efforts to prepare the proceedings of the conference on a fast track in a span of 4 months are laudable. It provides a good coverage of all presentations and a generous placing of the photographs is an added attraction. It is sincerely hoped that this document provides an update on rabies in Asia and the professionals and scientists find this useful and interesting. It is also planned to host this on the website of Rabies in Asia Foundation viz. www.rabiesinasia.org for wider dissemination.

I sincerely thank Government of Vietnam for giving us an opportunity to organize this scientific event in Hanoi. The advice and guidance of Dr. F.-X. Meslin, World Health Organization, Geneva, Switzerland deserves a special mention without which this event would not have been possible. The support of Novartis Vaccines, Sanofi Pasteur, Merial SAS, Zydus Cadila and others is gratefully acknowledged. Lastly, the help of my fellow trustees, Chairpersons of countries chapters and advisors of RIA Foundation is sincerely acknowledged.

Dr. M. K. Sudarshan, MD, FAMS
WELCOME SPEECH

Dr. Trinh Quan Huan
Vice Minister
Ministry of Health, Vietnam

Dear Dr. F. X. MESLIN, WHO, Geneva, Switzerland
Dr. M.K. Sudarshan, President - Rabies in Asia Foundation, India
Dr. S.N. Madhusudana, Director, Publications
Representatives of ASEAN Secretariat
Distinguished Guests, Speakers; Ladies and Gentlemen,

On behalf of the Ministry of Health, Vietnam, I would like to express our warmest welcome to all of you to the 2nd meeting RIACON 2009, VIET NAM CHAPTER held by The National Institute of Hygiene & Epidemiology (NIHE).

Rabies is considered as a neglected infectious disease. It should request stronger attention from government and animal care system. With a crucial transmission method from animal (e.g. dog, cat) to human and case fatality rate of 100%, rabies is being a major public health problem not only in developing countries, especially in ASIA and AFRICA, but also in developed countries. Therefore, the effective combination between prevention and control measures aimed to eliminate the rabies from both animal and human health system are essential requirements. The conference “Rabies in ASIA-Vietnam Chapter 2009” will be a great opportunity to bring scientists and experts together to simultaneously share information and experience, concurrently update knowledge and search for international collaboration targeted to rabies elimination worldwide.

This is the 2nd meeting RIACON 2009, VIET NAM CHAPTER after the first one hold in India two years ago funded by both Sanofi Pasteur and Novartis Vaccines Companies.

The targets of the 3 day workshop are to enable scientists from International organizations, agencies, institution from both government and non-governments, especially ASIA countries to access to the most recent update information of rabies prevention and control methods, vaccine development and technology, technical issues sharing from each countries and sub-continents. The workshop will touch to the current challenging of rabies on the updated practices in human and animal rabies control, human rabies diagnosis and prevention, sharing the fundamental and implementation research

We are looking forwards to the successes of the workshop. To reach this target, it is our honor to receive the excellent assistance from WHO headquarter in Geneva,
Switzerland, Rabies in Asia Foundation in India and financial support from Sanofi Pasteur and Novartis Vaccines Companies. Sincerely thank the participation and contribution of all experts, scientists, guests in the workshop.

I believe that the workshop will be an excellent chance to discuss and share experiences, achievements which usefully contribute to improve rabies control, prevention in the region and each ASIA country.

Very best wishes to all of you productive working sessions and enjoyable stay in Hanoi, Viet Nam

Thank you
Dear Prof. Trinh Quan Huan, Vice Minister, Ministry of Health, Viet Nam
Dear Prof. Nguyen Tran Hien, Director of National Institute of Hygiene and Epidemiology (NIHE)
Dear Dr M.K. Sudarshan, President and Dr A. Narayana, Executive Director, Rabies in Asia (RIA) Foundation,
Dear Drs Luningning Villa and Khin Devi Aung, Representatives of the ASEAN + 3 Emerging Infectious Diseases (EIDs) Programme,
Dear Drs M. Attlan, F. Borgese and NIHE Secretariat especially Dr Nguyen Thi Kieu Anh with whom this meeting would have not been possible,
Distinguished Guests, Speakers, Colleagues and Friends,

It is my pleasure to be with you and to represent the World Health Organization at the occasion of this Rabies in Asia Conference, the second held in Hanoi. Though advances have been recorded since the first Hanoi meeting of 2001 human rabies particularly dog-mediated human rabies remains a disease of public health and economic significance in most parts of Asia. Even today countries of central, east and south Asia are at different stages of their fight against this dreadful disease: in some the human rabies is on the decrease as a consequence of targeted interventions while in others rabies has been spreading unabated in dogs with more reported human victims. In this context event like this international conference bringing specialists and scientists from many different countries (from Iran to the west to Japan on the east) and disciplines together to share their experience in combating rabies in both humans and animals and to learn about new technological and strategy developments is extremely useful. The World Health Organization looks forward to reviewing the outcome of your deliberations. It has been very rewarding for me to collaborate with both NIHE and RIA in the preparation of the scientific programme of the conference. The efforts of all those who have made this meeting possible particularly NIHE, RIA Foundation and its partners should be commended.

Considering the rather full scientific and social programme prepared for us by our hosts, I am sure we will all enjoy both our participation in the meeting and stay in Hanoi. I wish us all a very successful meeting.
OPENING REMARK

Dr M K Sudarshan,
President, RIA Foundation and
Principal & Professor of Community Medicine,
KIMS, Bangalore, India

Dr. M K Sudarshan mentioned about formation of Rabies in Asia Foundation in December, 2005 at Mumbai during a meeting of rabies experts from the countries of Asia, Europe, WHO, CDC etc., where it was resolved to form this association. The group authorized the Indian team present to establish & hold the first conference. Consequently, on 1st April, 2006, the Rabies in Asia [RIA] Foundation was registered in Bangalore, under the Indian Trust Act.

Dr M K Sudarshan also mentioned the Aim & Objectives of the RIA Foundation. He also mentioned the formation of the country chapters in Bangladesh, China, India, Pakistan, Philippines, Sri Lanka, Thailand & Vietnam.

He mentioned the various activities of RIA Foundation & country chapters:

1. 1st RIA Conference (RIACON) which was held from 3-4, March, 2007 at NIMHANS, Bangalore, India
2. 2nd RIA Conference (RIACON) which is being held from 9-11, September, 2009 at NIHE, Hanoi, Vietnam
4. Production of a video film “Rabies: A fatal but preventable disease”
5. He requested the members present to visit www.rabiesinasia.org for more information on various other activities of RIA Foundation.
RELEASE OF RIA FOUNDATION VIDEO FILM ON “RABIES - A FATAL BUT PREVENTABLE DISEASE”

Dr. Trinh Quan Huan
Vice Minister, Ministry of Health, Vietnam
Group photo
The Second Rabies in ASIA Conference-RIACON 2009
Hanoi, Vietnam 9-11 September 2009
SESSION 1. OVERVIEW OF RABIES IN ASIA
COUNTRY AND SUB-CONTINENT REPORTS

OVERVIEW OF RABIES IN ASIA

Chair person: Dr. M.K. Sudarshan, President RIA Foundation, India
Co-Chair person: Prof. Quing Tang, CDC, China
Reported by Dr Sudarshan, , President RIA Foundation, India

- Dr. M.K. Sudarshan in his opening remarks lauded the efforts of NIHE, Vietnam in organizing this 3 days event. He pointed out that ASEAN as a body of cooperation is working excellently for elimination of rabies in its member countries by 2020. Likewise, there is a need for similar efforts by SAARC in South Asia where a very high burden of rabies exists.

- Dr. Betty Dodet presented the gradual change in scenario of rabies in Asia since 2001 and spoke about informal groups of AREB, RIA, ARC, PRP etc.

- Dr. L. Villa informed about the role & activities of ASEAN for elimination of rabies by 2020 in all member countries from SE Asia.

- Dr. Wada presented the successful story of dog rabies control through national mass dog vaccination campaign in Brazil.

- Dr. Richard Franka spoke on historical aspects since the era of Pasteur to the present scenario to the future where climate change was linked to migration of animals, role of OVRS.

Recommendations:

The history of improved situation of rabies in countries of Asia through various efforts in these countries must be kept in mind for future planning of rabies program. The ASEAN secretariat should continue to assist its member states to eliminate rabies by 2020.

The successful campaign of mass national vaccination campaigns of dogs for elimination of rabies in Brazil may be considered as a successful model which may be considered for replication by other countries in Asia. The effect of climate change on movement of animal reservoirs of rabies in Asia must be considered for any actions in the future for control of rabies in animals.
Rabies in Asia: Evolution of the situation since the Asian rabies meeting, Hanoi 2001

B. Dodet & the Asian Rabies Expert Bureau (AREB)
Representative of AREB, Australia
betty.dodet@dodetbioscience.com

In March 2001, an international symposium on rabies was held in Hanoi. It was the last in a series of meetings organized by the Merieux Foundation with the co-sponsorship of the World Health Organization (WHO) in Central and South-East Asia. Resolutions were issued at the end of the symposium, urging those countries still producing nerve tissue vaccine to discontinue their production by 2006 and to develop, with the help of WHO, policies for administering post-exposure prophylaxis (PEP) with cell culture vaccines (Resolution 1). The Symposium also urged governments to consider early vaccination of infants and children in countries or regions where canine rabies has not yet been controlled (Resolution 2); and WHO to establish an informal group of rabies experts, representatives of Asian countries, rabies vaccine manufacturers and other relevant partners, to be advised on best strategies for the control and elimination of human and canine rabies in Asia (Resolution 3).

Since then, India, Nepal and Vietnam have discontinued the production of nervous tissue vaccine and now recommend the use of cell culture vaccines. A decrease in human rabies mortality has been observed in countries such as the Philippines, Sri Lanka and Thailand, which have implemented rabies control programs. However, canine rabies is still present in these countries, some Asian countries have not yet adopted rabies control policies and sheep brain vaccine is still produced in Pakistan and Bangladesh; the prevalence of rabies has been expanding in some regions, e.g. in Bali, formerly a rabies-free island, and China has reported an increase in the incidence of human rabies deaths.

Asian rabies experts have been very active in the fight against rabies, and have established networks, such as the Rabies in Asia (RIA) Foundation and the Asian Rabies Expert Bureau (AREB), an active network established in 2004 that meets on an annual basis. They try to find solutions to issues specific to the rabies situation in their countries, conduct multi-country surveys, and deliver recommendations. Reports of their meetings are published in international journals.

Strategies for rabies elimination in South East Asia have been designed and discussed in workshops. Expert consultations on rabies have been conducted at the WHO headquarters in Geneva, the next one scheduled to be held in October 2009. 2007 was an important year for rabies. The first scientific Rabies in Asia Conference (RIACON), organized by the RIA Foundation in Bangalore in March 2007, was followed by the OIE/WHO/EU international conference Towards the Elimination of Rabies in Eurasia, in Paris. It is significant that this meeting was jointly organized by international...
organizations for human and animal health.

The same year, the creation of the Alliance for Rabies Control (ARC) and the establishment of a World Rabies Day (WRD), was a major achievement for rabies. Over 85 countries last WRD, with many initiatives taking place in Asia. The ARC has been active in coordinating partners, to help implementing programs and pilot projects (e.g. the Bohol Rabies Prevention and Eradication Program, a cooperative effort of the ARC, the Bohol Provincial Government and a Private Swiss Foundation; the Partners for Rabies Prevention Group). WHO coordinates a project funded by the Bill & Melinda Gates Foundation, aiming at the elimination of canine rabies in Visayas Islands.

Also in 2007, the Philippines enacted into law the Anti-Rabies Act, strengthening the existing National Rabies Prevention and Control Program with the aim of eliminating rabies by 2020. The resolution of eliminating rabies by 2020 was also adopted by the ASEAN Plus Three Countries in 2008, which indicates an increasing political involvement that is crucial for rabies elimination.

The road is still long, but there are excellent reasons for hope.

Reasons for Hope

2004: Establishment of AREB – First annual meeting of AREB
2006: Establishment of the Rabies in Asia Foundation
2006: Establishment of the Alliance for Rabies Control (ARC)
2007: First Rabies in Asia Conference (RIACON)
2007: OIE/WHO/EU Intl conference Towards the Elimination of Rabies in Eurasia
2007: First World Rabies Day
2007: The Philippines enact into law the Anti-Rabies Act
2007: Vietnam: decree enacts a rabies elimination program
2008: Creation of the Partner for Rabies Prevention group
2008: Resolution of eliminating rabies by 2020 adopted by the Asean Plus Three Countries
2009: Rabies retained in the final list of GAVI investment case (even if finally not selected in current economical crisis environment)
Call for Action towards the Elimination of Rabies in the ASEAN Plus Three Countries by Year 2020 and ASEAN Plus Three Advocacy Strategies

MA. Luningning P. Elio Villa  
Programme Facilitator  
ASEAN Plus Three Emerging Infectious Diseases Programme  
luningning@asean.org

Under the purview of the ASEAN Plus Three Emerging Infectious Diseases Programme, the Workshop on Strengthening Cooperation and Information Sharing on Rabies among ASEAN Plus Three Countries was organized by the National Institute of Hygiene and Epidemiology, Ministry of Health, Viet Nam held in Ha Long, Viet Nam on 23-25 April 2007.

Recognizing the need for political commitment and action at the highest level of all ASEAN Plus Three Countries to consider rabies as one of the priorities and an important emerging and re-emerging disease and to provide resources for human and animal health services, experts and representatives from the human and animal health sectors from the ASEAN Plus Three Countries (China, Japan and Republic of Korea) and from relevant organizations put forward a Call for Action for the Elimination of Rabies in the ASEAN Member States and the Plus Three Countries by Year 2020.

Recommendations for implementation at the national level and at the regional level included in this call focused on the following areas: a) policies/legislation 2) prevention and control of rabies in animals and prevention in humans 3) surveillance 4) integration, coordination and partnership 5) public awareness and communication 6) training; and 7) research

The Call for Action was also presented to the ASEAN Sectoral Working Group on Livestock (ASWGL) for endorsement by the ASEAN Plus Three Agriculture and Fisheries Meeting. A copy of this document was also provided to relevant organizations like FAO, OIE, WHO and other relevant institutions for their information and action, as appropriate.

The ASEAN Plus Three Health Ministers in their Meeting held in October 2008 in Manila, Philippines expressed support for the Call for Action towards the Elimination of Rabies in the ASEAN Member States and the Plus Three Countries by year 2020. The Health Ministers requested the ASEAN Plus Three EID Programme to develop a regional strategic framework for the prevention and control of rabies in the ASEAN and the Plus Three Countries in accordance with and in support of guidelines of the WHO and international standards for animal disease control and surveillance of World Organization for Animal Health.
To operationalize the Call for Action for the Elimination of Rabies in the ASEAN Member States and the Plus Three Countries by Year 2020, the ASEAN Plus Three Emerging Infectious Diseases Programme continues on with the project Strengthening Rabies Programs of the ASEAN Plus Three Countries.

A study tour in the Philippines, participated by the animal and human health representatives from Cambodia, Lao PDR, Indonesia, Myanmar, Viet Nam and China and by the World Health Organization and Bill Gates Foundation, was conducted in the Philippines to showcase the initiatives for rabies prevention and control strategies from the national to the local level with involvement of other sectors and communities. The study tour was meant to contribute to the development or strengthening of rabies programmes in the ASEAN Plus Three Countries, notably on human and animal health collaboration and involvement of other sectors.

Organized by the National Institute of Hygiene and Epidemiology (NIHE), Ministry of Health, Viet Nam, the ASEAN Plus Three Workshop on Strengthening National Rabies Programmes and attended by international and regional rabies experts and participants from the ASEAN Plus Three Countries and other relevant Organizations, was held on 7-8 September 2009 back-to back with Rabies in Asia Conference (RIACON) in Hanoi, Vietnam. Delegates shared their country work plans and developed a regional framework in strengthening rabies and prevention control through development of multisectoral system/mechanism of information exchange and collaborative efforts at the national level and regional level.

**Year 1 Project:**
**Strengthening Cooperation and Sharing Information on Rabies among ASEAN Plus Three Countries**

**Year 2 Project:**
**Strengthening Rabies Programme in the ASEAN Plus Three Countries**

**Proponent:** Viet Nam  
(Institute of Hygiene and Epidemiology)
Rabies is a zoonosis with approximately 100% mortality rate. During 1980 to July 2009, there were reported 1,445 human rabies cases in Brazil. In 1973 was created the National Program to control rabies to reduce rabies transmitted by dogs and many activities were implemented. Massive campaigns were done in dogs and cats, capture of animals without owner, monitoring viral circulation, human rabies prophylaxis, and education in health were activities realized for urban cycle. Other activities are being done in wildlife animals, mainly in hematophagous bats.

In 1980 were reported 173 human rabies cases and in 2009 one case is registered. In 1998, 1,737 rabid dogs were reported and in 2008, 36 dogs with rabies. Coverage over than 80% in massive campaigns is occurring since 1993 and a strategy to develop a second campaign is implemented in 2001 for risk municipalities. In 2009, a culture cell vaccine is being acquired for risk area and in 2010 will be implanted in all Brazilian states.

The sylvatic cycle is emerging, and in 2004 and 2005, an outbreak of human rabies cases occurred in Amazonic region with 62 cases transmitted by vampire-bats. A passive surveillance for wildlife is an important tool to detect earlier the viral circulation and block rabies focus.

Human rabies prophylaxis is very important and around 420,000 persons are attendance by year and approximately 270,000 persons received at least one dose of culture cell vaccine. In 2008, the first cure in human was reported in Brazil, this patient was submitted to Milwaukee protocol modified.

In conclusion, human rabies cases are decreasing in Brazil, but it continues being a serious public health problem. The sylvatic cycle is becoming the mainly problem for rabies in Brazil. These findings highlight the importance of improving access to health care, the need of health education and adequate surveillance system for rabies control.
In the 21st century, rabies remains incurable. Human pre- and post-exposure prophylaxis together with vaccination of domestic and wildlife animals are currently the most efficient interventions. Despite significant improvements in our understanding of Lyssavirus pathobiology, a progress in basic understanding of vaccine immunogenicity and efficacy and advances in rabies biologics production globally, the practical applicability remains unevenly distributed and restricted by local economic and technical limitations. Modern vaccines and immune globulins remain largely unavailable or unaffordable in the majority of rabies endemic countries without a suitable infrastructure and animal rabies prevention programs. A priority of current research and public health policies should focus upon the development of relevant de-centralized laboratory-based surveillance programs, and the design and production of inexpensive, safe and efficacious biologics and vaccination regimens. Development and application of relevant animal models as human surrogates is critical to provide useful inferences to the continued improvement of rabies prophylaxis and development and evaluation of experimental treatment protocols. New candidate oral rabies vaccines and a renewed immunocontraceptive approach to population management will facilitate animal prevention and control programs in both the developed and developing world.
**Laboratory Techniques in Rabies**

- Virus Isolation
  - Mouse Inoculation
  - Cell Culture

- Molecular Techniques
  - RT-PCR Sequencing

**Antigen Detection**

- Direct fluorescent antibody (DFA) test
- Indirect fluorescent antibody test (mAb typing)
- Direct rapid immunohistochemistry test (DRIT)

**Post-exposure prophylaxis (PEP)**

- Passive immunization - Immune globulins
  - von Behring and Kitasato
  - Sheep and horse rabies immune globulin (ERIG)
  - Human rabies immune globulin (HRIG)
  - F(ab)2 fragments
  - Monoclonal antibodies (mABs)?
RABIES SITUATION IN NORTH-EASTERN ASIAN COUNTRIES

Chairperson: Dr. F.X. Meslin, WHO
Co-Chair Person: Dr. B. Dodet, Representative of AREB
Reported by: Dr. B. Dodet, Representative of AREB

Reports from China and Japan showed contrasted situations.

China

After a decrease down to <200 cases in 1996, reported rabies cases have been increasing steadily to peak at 3300 reported cases in 2007. Then it started decreasing. Most rabies cases are in 3 southern provinces: Guangxi, Guizhou, Guondog, Hunan and Sichuan. Dog is the main transmitter. High incidence of rabies is in dogs living in this area. Virus phylogenetic studies can give indications on rabies virus circulation through dog movements.

The low role of canine immunization, lack of awareness of the population and inadequate PEP are responsible for the high rabies incidence.

Japan

Japan eliminated rabies in the 50s and only imported human cases (1 in 1970 and 2 in 2006) were reported. Sustained efforts have been necessary to keep Japan free from rabies e.g. compulsory registration and rabies vaccination of dogs, quarantine for imported animals. Control and prevention of rabies in neighboring countries, where rabies is endemic, is important for maintaining a rabies free state in Japan.
Human rabies cases keep increasing in China in recent years and have reached the highest peak in 2007. The human rabies cases reported in China between 1996 and 2008 predominately occurred in the rural areas and mainly involved the peasants, students and unattended children. Over 60% of the total human rabies cases nationwide were reported in Guangxi, Guizhou, Guangdong, Hunan and Sichuan provinces. 85-95% of human rabies cases were exposed to dogs and 4-10% of them were exposed to cats, reporting human rabies cases exposed to the wild animals were increased in recent years. The low rate of canine immunization, lack of awareness and inadequate post exposure prophylaxis (PEP) of humans were the main factors leading to the high incidence of human rabies in China.

By the end of year 2006, the total population of China is 1,314.48 million, the incidence of rabies in 2006 is 0.2518/100,000.
Human rabies distribution in China, 2008

2008年全国狂犬病病倒数（分省）

The highest epidemic provinces are Guangxi(372), Guangdong(319), Guizhou(281), Hunan(229) and Chongqing(173), the case number of these five provinces account for 55.72% of whole country’s cases.

Proposed strategy for rabies elimination

- Government commitment and financial support
  - Improve the control of canine rabies
    - Immunization and management
  - Strengthen the training of PEP on local health care workers
- Call the awareness of public and spread useful prevention knowledge
- Promote the use of practical technique in China
  - Inactivated animal vaccine
  - Monoclonal antibody
Rabies Prevention in Japan

Dr. Satoshi INOUE
Department of Veterinary Science, National Institute of Infectious Diseases
sinoue@nih.go.jp

Japan has been free of rabies for most of half century. The last case of indigenous human and animal rabies was in 1954 and 1957, respectively. In 1970, a college student suffered from rabies in Tokyo after a trip to Nepal where he had been bitten on the right rural region by a stray dog. Recently, in November 2006, two patients with a history of dog bites in the Philippines were suspected of rabies at the hospitals in Kyoto and Yokohama. Definitive diagnosis of rabies was carried out within 24 hr of sample submission by the conventional ante-mortem diagnostic techniques in our laboratory. Rabies virus (genotype 1) was identified in the saliva by the reverse transcription-polymerase chain reaction (RT-PCR). The presence of virus antigen in the formalin fixed tissue from nape of the neck was confirmed by the immunohistochemistry (IHC). Subsequent phylogenetic analysis of the amplified viral gene demonstrated that both isolates were closely related to canine rabies variants circulating in the Philippines. The events concerning on these imported rabies cases were dealt in accordance with the 2001 Rabies Contingency Plan (MHLW, Notification in 2001, and supplement in 2003), in terms of the initial response and medical practice. In a country where rabies is rare it is still important to validate the existing rabies diagnostics. In Japan, under Rabies Prevention Law (MHLW, 1950, and amended in 1999), Domestic Animal Infectious Diseases Control Law (MAFF, 1951, and amended in 2005) and Infectious Diseases Control Law (MHLW, 1998, and amended in 2008), substantive efforts to prevent rabies have been adopted by central and local governments, relevant ministries, various concerned bodies, veterinarians, and physicians (e.g. registration and rabies vaccination of dogs, control of stray dogs, import and export quarantine of animals, appropriate PEP for human, enlightenment program such as WRD). The follow-up amendment and drill of measures and contingency plan is also deemed necessary, because any inappropriate public health response or delay at an early stage of rabies cases, even those in doubt, leads to unnecessary, excessive social anxiety. As more than 17 million overseas travelers visiting foreign countries every year, providing necessary information against rabies is very important. The intelligible explanation during education and enlightenment based on the evidence of epidemiology and pathogenesis is helpful for the understanding of rabies by the public. The control and prevention of rabies in developing countries is also very important in maintaining a rabies free status in Japan. In this regards, the cooperative rabies research through the laboratory net work in Asia should be enhanced.
### The indigenous rabies in Japan (1941-1957)

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</tr>
</tbody>
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### National Government

**Ministry of Health, Labour and Welfare**
- Quarantine Station
- Notification System for Importation of Animals (mice, ferret, mammals other than dogs etc.)
- Ordinary Measures
  - Communication, Coordination
  - Cities, Towns, Villages (Local Government of municipality level)
    - Dog Registration (once a life)
    - Presentation of vaccination certificate
- Dog Owner
  - Vaccination certificate
    - Rabies vaccination (every year)
- Veterinarian
  - Rabies Outbreak Notification

**Ministry of Agriculture, Forestry and Fisheries**
- Animal Quarantine Service
  - Import/Export Quarantine (dogs, cats, racoons, foxes and skunks)
- Report
  - Advice, Guidance
- Outbreak Response
  - Notification
  - Isolation
  - Prohibition of Extermination
  - Handing over the body
  - Measures to identify types of disease
  - Public announcement and order of enchainment
  - Examination and preventive vaccination
  - Movement restriction or road blocking
  - Other measures

**Prefectures, ordinance-designated cities (Local Government)**
- Health Center, Center for Animal Management
- Rabies Prevention Official (Vet.) 2,262 officials (2007)
- Rabies Prevention Technical Officials
- Capture and Detention of unregistered or unvaccinated dogs 73,303 head (2007)
- Issuance of a dog tag 6,739,716 head (2007)
- Issuance of vaccination Certificate tag 5,097,615 head (2007)
Rabies in South Western Asia

Chairperson: Dr. Prof. Nguyen Tran Hien, Director, NIHE
Co-Chair Person: Dr. Raffy Deray, National Rabies focal point, Philippines
Reported by: Dr. Raffy Deray, National Rabies focal point, Philippines

- Rabies is indeed a public health problem in South Western Asia,
- Rabies is present in all 5 countries
- Incidence of human and animal rabies is based on estimate,
- Rabies is not notifiable
- Surveillance is inadequate
- Dog bite is still the main mode of transmission of rabies to human,
- Dog is the still the main reservoir of rabies, Mention of other animals: Jackals, mongoose etc.
- Post Exposure Prophylaxis: Tissue culture vaccines (Modern), PCEC, PVRV and PDEV available in all 5 countries, PEP Coverage is still low
- HRIG & ERIG: Available in all countries, Issue on availability & affordability
- Problems/ Issues with adequacy and affordability, 2 countries still use Nerve tissue vaccine: Pakistan & Bangladesh
- Pakistan < 50% PEP Coverage
- Dog Vaccination is a question, Low vaccine coverage

Reasons for Human Rabies:

- Lack of awareness (Community, health workers), inadequate knowledge of health workers
- Inadequate TCV/ RIG, Expensive, Limited/ not always available, Poor compliance to PEP
- Delayed, Negligence, Traditional healers, Lack of awareness
- Reasons for Canine Rabies, Low vaccination coverage, Problems on stray dogs/ animals
- Inadequate veterinary services, Not enough veterinarians in the private sector
- Wildlife reservoir, Less value for animals, Animal rabies
- Rabies Prevention and control activities
- Dog vaccination, Dog population management, Sterilization: Surgical & Medical (Progesterone)
- Control of stray dogs
- Human rabies- Provision of post exposure prophylaxis, Training on bite management
- Program Activities: Human and Animal Rabies Prevention
- Health education / promotion
- Increasing government support and involvement
- Involvement of NGOs: RIA foundation
Pakistan has a population of an estimated 180 million. 67.5% of the population is rural. Although there are no accurate data, it is estimated that there are over 25,000 animal bites/year and 2000-5000 rabies deaths a year. We are now in process of carrying out a detailed one year national dog bite and surveillance. Results should be forthcoming in mid 2010. Over 90% animal bites are from dogs, other animals being cats, cattle and wolves. Most bites occur in rural areas, however majority of victims do not seek medical attention and use home remedies.

Sheep brain vaccine is still produced and used in government run hospitals; however because of increased awareness imported cell culture vaccines (CCV) are fast replacing the sheep brain vaccine. Most institutions use intramuscular CCV, but in 3 of Karachi's largest hospitals and another in the province of Sind TRC regimen are being regularly used. Equine rabies immune globulin, though available, is used infrequently because of high cost of the product. Knowledge, application and practices of general practitioners are generally very poor.

Only pet animals are vaccinated under care of private vets, whereas stray and feral dogs roam freely and are unvaccinated. There is an enormous need for public and physician awareness in Pakistan. Through individual and collaborative efforts of members of Rabies in Asia Pakistan Chapter there have been attempts at mass awareness through print and electronic media, large participation in rabies awareness walks and other activities on World Rabies Day 2007 and 2008 and distribution of pamphlets and video docudrama. For physicians there have been over 20 lectures and hands-on training workshops with distribution of the recently published Guidelines for Prevention of Human Rabies. A National Conference on Rabies is in planning for October 1, 2009, in the presence of the Federal Health Secretary, with delegates from over 20 cities.
In Nepal, most (94%) of the human cases follow contacts with rabid dogs. It is estimated that 200 people on an average die annually due to rabies. National Statistics shows that about 30,000 people receive post treatment and about 55000 dogs are immunized against rabies with a tissue culture vaccine produced in the country. There is only one diagnostic laboratory in the country which is located in Kathmandu under Department of Livestock Services. At present the tissue culture vaccine is used for post exposure treatment in dog only. There is no tissue culture vaccine production in human use in the country and it has to be imported.

Epidemiological surveillance study was carried out during the year 2005 to 2007 throughout the country supported by Donative Unit Rabies Vaccine to Nepal (DURVN) Tokyo, Japan and DDJ Research Foundation, Nepal. Suspected rabid dog bite human cases recorded and reported by different media and survey team of NZFHRC were 16812, 16401 and 20943 for the year 2005, 2006 and 2007 respectively. The mortality (i.e. death cases of human) of human hydrophobia cases was 1.5%, 1.4%, and 2.17% during the year 2005, 2006 and 2007 respectively.

From 2002 to 2008 (till to date) free dog rabies vaccination in 26 municipalities out of 58 municipalities of the country has been carried out by NZFHRC. In 2007 a workshop for "Consensus Building among National Alliance Partners to Eliminate Canine Rabies in Nepal and Development of Strategic Plan" was organized and supported by World Health Organization (WHO). Government of Nepal Operational Plan (2007-2012) for rabies control has been approved for its implementation. The Alliance Group for Rabies Control in Nepal comprising Department of Livestock Services, Veterinary Public Health Division; Kathmandu Metropolitan City (KMC), Department of Public Health and Social Welfare; Kathmandu Animal Treatment (KAT) Centre and National Zoonoses and Food Hygiene Research Centre (NZFHRC) has been formed.

Keywords: Rabid dog, Alliance group, Canine Rabies, Strategic Plan
Components of short term and long term activities to be carried out in different phases:

- Social mobilization and communication
- Vaccine production
- Diagnosis
- Programme management
- Policy
- Surveillance and outbreak management
- Training programme
- Inter and intrasectoral co-ordination
Sri Lanka is an island with an extent of 65000 sq. km. which is situated in the Indian Ocean. The population of the country is about 19.4 million as stipulated by 2001 country wide census. Ministry of Healthcare & Nutrition is the responsible body in the country for Rabies control and the activities are mainly conducted through the Public Health Veterinary Services (PHVS), involving the decentralized health system. Provincial, Regional Directors of health, Medical officers of health, Public health Inspectors and Certified dog vaccinators are mainly implements the program island-wide.

Dog is the main reservoir of rabies, as majority of the human deaths were due to dog bites and the majority of the positive animal heads for rabies were dogs. Estimated number of the dog population is 2.5 million. We have not estimated the population of other animal reservoirs such as mongoose and Jackals. Community survey that has been conducted in 1997 and it has revealed that incidence of dog bites was 13.2 per 1000 population (1.3%). Analysis conducted in 2008 has revealed 7.55 per 1000 (0.75%) population have initiated with Rabies Post Exposure Treatment (PET) in the year 2003. PCEC and VERORAB Human vaccines are used for Rabies PET and 343000 Vials has been used in 2008. Intramuscular and intra-dermal regimes are used in deferent institutes. Over 95% of patients are treated with ID 2site schedule. Equine rabies immunoglobulin and Human rabies immunoglobulin used to treat major exposures. In 2008 123730 vials of ERIG and 3570 of HRIG has been used for PET.

Mass rabies vaccination owned dog, Stray dog vaccination using a special device called 'Auto Plunger', Surgical and chemical animal birth control (ABC), Conduction of awareness program., Training of all relevant categories of health staff., Promotion of collaborative partnership with relevant stakeholders (Animal welfare NGOO, Livestock, Local government and Private sector and Monitoring and evaluation of all activities are major activities conducted for rabies control in dogs.

Highest number of dog vaccinations achieved was in year 2008. Coverage was 45% when dog population is worked out at the ratio of 1 : 8. Total of 1,103,258 dogs were vaccinated against rabies in 2008. In addition Private veterinarians also vaccinate estimated Number of 100,000 dogs. Raksharab-India, Rabisin-France, Intervet-Holand are the Main rabies vaccines used in the country.

In the year 2007 dog elimination was completely stopped and government allocated
Rs 100 million (U$ 1 million) to conduct surgical dog sterilization island wide in 2008. As a result 190084 dogs were surgically sterilized and 85457 stray dogs were injected with Medroxy progesterone acetate.

In the year 2008, 51 people died of rabies. 42 human rabies cases are due to Dog Bites. Cats, Rock squirrel, Bandicoots bites are the cause for balance 9 deaths.

Negligence of animal bite victim; mostly children, drug addicts, drunken persons, beggars, Lack of knowledge among the community about the possibility of transmission of rabies through animals other than dogs such as Cats, Bandicoot, Rock squirrel, Mongoose and Treatment failures due to application of 8 site schedule in place of Immunoglobulin are main reasons for presence of human rabies.

The main reasons for animal rabies deaths are higher percentage of stray dogs (20%) and owned dogs not confined (60%), Inadequate coverage of dog rabies vaccination (49%) due to inadequate infrastructure, logistic & manpower facilities to conduct rabies control activities and presence of wild life reservoirs (Mongoose and Jackal) very closer to stray dog habitat. In 2008 681 dogs, 62 cats, one mongoose and 13 cows has been confirmed as rabies positive by the three laboratories located in Colombo, Gall and Peradeniya.
<table>
<thead>
<tr>
<th>Strategies</th>
<th>Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Immunize all dogs (domestic, community and stray) through mass vaccination campaigns to achieve 75% coverage of dog population.</td>
<td>Conduction of dog immunization programs</td>
</tr>
<tr>
<td>2. Encourage the participation of both private and public sector veterinary services in providing dog sterilization and vaccinations to dogs.</td>
<td>Get support of animal health sector in the govt and private sector. – promotion of private and government partnership</td>
</tr>
<tr>
<td>3. Sterilize dogs through appropriate chemical and surgical methods.</td>
<td>Female dog sterilization</td>
</tr>
<tr>
<td>4. Control of environmental conditions in public places conducive to propagation of dogs.</td>
<td>PHIs garbage management with local authorities.</td>
</tr>
<tr>
<td>6. Develop a mechanism to identify and dispose of all suspected or rabid animals.</td>
<td>Advocacy to local authorities for Local isolation facilities to be set up</td>
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<tr>
<td>7. Strengthen the Rabies surveillance system.</td>
<td>Support provincial animal laboratories for Dog rabies surveillance</td>
</tr>
<tr>
<td>8. Enact appropriate legislation to implement the national rabies policy.</td>
<td>Advocacy to expedite approval of new Act on Rabies Control and responsible dog ownership.</td>
</tr>
<tr>
<td>9. Strengthen the governance and stewardship for Rabies elimination.</td>
<td>National and Provincial monitoring system using the given indicators to be strengthened</td>
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Rabies in Bangladesh

Dr. Shafiqur Rahman
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Institute of Epidemiology, Disease Control & Research (IEDCR) Bangladesh
we_shafiq_rukhsi@yahoo.com

Bangladesh with a land of 144 thousand square kilometer, and population density of 939 per square kilometer is located in South Asia. In 2008, the annual population growth rate was 1.7 percent with a male to female ratio of 105:100. The per capita gross domestic product (GDP) of the country is US$ 526 in 2009. Life expectancy at birth is 65.4 years for both sexes. The number of physicians and nurses rendering health services are 38,537 and 15,023 respectively. Three apex institutes - Institute of Public Health (IPH), Institute of Public Health Nutrition (IPHN), and Institute of Epidemiology, Disease Control and Research (IEDCR) - are providing specialized public health services in the country. These institutes are managed by the Government of Bangladesh. Besides, curative and preventive healthcare services are rendered by hierarchy of health facilities in both public and private sectors. About 78.4 percent of the major communicable and non-communicable diseases afflicting the population include diarrhea disease (14.7%), helminthiasis (10.6%), skin diseases (9.1%), anemia (7.5%), acute respiratory infection (7.1%), peptic ulcer (6.6%), nutritional deficiency diseases (6.5%), pyrexia of unknown origin (4.4%), eye disease (3.4%), injuries (2.8%), ear diseases (2.2%), dental diseases (2.0%), asthma (1.5%), and 'others' (21.5%). Presenting the major diseases in descending order of occurrence, it is observed that rabies - a viral neuroinvasive zoonotic disease - is not included within 78.4 percent of the diseases. Rabies has less than 1.5 percent coverage of the total disease profile of the country, which is included in the 'others' category of the major diseases. Rabies cannot be belittled on the basis of its occurrence in a densely populated country like Bangladesh. As rabies has almost 100 percent fatality and is a preventable disease, it is of public health importance. In Bangladesh the annual estimated number of human rabies death is 10,000, though few records frequently underrate the figure. There are an estimated 55,000 human deaths annually from rabies worldwide, with about 31,000 in Asia, and 24,000 in Africa. Annual number of animal bites/exposure rates in Bangladesh is estimated to be more than 100,000. About 95 percent of the reservoir animal of rabies is stray dog, while cat, jackal, mongoose... cover the rest 5 percent in the country.

In human, administration of vaccine is advised in suspected rabid animal bite without bleeding, or licks on broken skin. Administration of both vaccine and immunoglobulin is advised in case of deep bite with bleeding. The phenolized sheep brain vaccine for human use is produced at and distributed through IPH, and is not available in the open market. It is used in post-exposure condition according to age and degree of severity of bite in dose of 0.5-1 ml injections administered intradermally around the umbilicus for 7-14 consecutive days. The sheep brain vaccine is much cheaper than cell culture vaccines, and is more frequently used compared to the other vaccines. Verorab, a
A purified rabies vaccine cultured on vero cells, is an imported product from Sanofi Pasteur, and is injected intramuscularly in post-exposure conditions in a dose of 2.5 IU (0.5 ml) on days 0, 3, 7, 14 and 30. Verorab is used in pre-exposure conditions too in same dose on days 0, 7, and 28. Booster injection, though infrequently practiced, is advised to be given 1 year later, and every 5 years. Rabipur, inactivated rabies virus vaccine, is also used in the country. It is an imported product from Novartis, and is used in post-exposure state in dose of 4 to 5 injections of 1 ml each at intervals over 3 or 4 weeks. In pre-exposure state 3 injections of the same dose is administered at intervals over 3 or 4 weeks. Human anti-rabies immunoglobulin produced by Bharat Serum and Vaccines Ltd is also imported in limited amount. The immunoglobulin is administered in post-exposure condition as a single dose of 20 IU per kg of body weight into the depth and around the wound as much as anatomically feasible, and any remainder is injected intramuscularly. Verorab, Rabipur, and immunoglobulin are not procured for distribution through the health facilities in public sector, but are available in limited scale in the open market in major cities. Phenolized sheep brain vaccine produced at the IPH is also used for animal in variable dose. Preventive vaccination is seldom done for pet dogs, but no vaccination for stray dogs and other reservoirs.

The main reason for human death due to rabies in Bangladesh is unawareness about vaccination, or if taken the course is not completed due to poor socioeconomic condition and unavailability in the vast rural area. Also the folk healers use unscientific management and delay appropriate post-exposure vaccination. The main reason for animal death due to rabies is related to the less importance attached to animal life in comparison to human life, and so animals are less frequently vaccinated. The animal handlers are less aware of animal rabies and take the help of veterinary folk healers who use unscientific post-exposure management.

Though notification of stray dogs to municipality/other concerned authority is mandatory in Bangladesh, but its implementation appear slack. The limited scope for early diagnosis and treatment of the post-exposed animal/human and cases is underutilized. In the capital city of the country, there is only one Infectious Disease Hospital (IDH) which is frequently inaccessible to the majority of the poor people in the rural area where most of the post-exposure events occur. Research on rabies is infrequently done in the country. Though phenolized sheep brain vaccine is produced at IPH, but its distribution is inequitable to the demand of the vaccination service facilities. New development in the field of rabies in Bangladesh include setting up of Bangladesh Animal Care, a society in private sector, that strives to educate the public on animal care to reduce and eliminate rabies and animal cruelty in the community. Another body, Association for Prevention & Control of Rabies in Bangladesh (APCRIB) is working with the global Alliance for Rabies Control, and the Government of Bangladesh to create awareness about rabies through organizing the World Rabies Day every year. For effective prevention and control of rabies in Bangladesh, further extensive research on social and ethological issues related to rabies need to be undertaken. Issues related to rabies need to be incorporated in the existing public health and livestock health surveillances of the country.
India, with a population of 1.13 billion, is the second most populous country. Rabies is endemic throughout and only the islands of Andaman & Nicobar and Lakshadweep are historically free of rabies. A recent WHO - APCRI survey (2004) revealed that annually an estimated 17 million animal bites and 20,000 human rabies deaths (2 per 100,000 approximately) occur. The dog (97%) is the principal vector followed by cats (2 %) and others.

In case of dogs and cats, being animals of no economic importance their vaccination coverage and population control are grossly neglected, leading to continued chain of transmission of disease. The vaccines available for dogs and cats include the indigenously produced BHK 21 Cell line vaccines (Raksharab, Rabivac Vet & Anirab) and vaccines imported (Ravvac 3, Defensor, Nobivac R, Imrab 3 & Rabies in). The pet dog population is about 28 million and an equal number are estimated to be strays. The coverage of vaccination in the domesticated dogs is very poor and thus poses a serious threat to household population. The control of stray dogs has recently become controversial and allegedly ineffective following the introduction of animal birth control (ABC) programme in the municipal areas of urban localities.

The currently available vaccines for humans include indigenously manufactured PCECV (abipur), PVRV (Abhayrab & Indirab), PDEV (Vaxirab) and imported Verorab (PVRV, from France). The RIGs available include indigenously produced ERIGs (Equirab, Vinrig & Abhayrig) and imported HRIG (Kamrab & Berirab-P). The coverage of human CCVs in animal bite victims is about 50% and RIGs about 2 % leading to the large number of preventable rabies deaths. There is virtually very little coordination between control of rabies in animals and prevention of rabies in humans.

The country stopped the production of sheep brain vaccine for humans in December, 2004 and switched over to exclusive use of CCVs in 2005. However, following the shortage of CCVs, in February, 2006 Government of India approved the use of intradermal rabies vaccination (IDRV) in Government hospitals. Presently, most of the states/provinces have switched over to IDRV for reason of cost effectiveness. In September, 2007 the revised national guidelines for rabies prophylaxis was evolved. In January, 2008 a Government of India pilot project on prevention and control of human rabies was launched in five cities to further augment the implementation of IDRV.
Assessing burden of rabies in India

- 20,000 (2 per 100,000 approximately) human rabies deaths annually.
- Animal reservoirs / vectors: Dog (97%), cat (2%) & others (1%) (mongoose, jackals, etc.).
- Pet/owned dog population - 28 million+.
- 17.4 million (17.4 per 1000 population) animal bites annually.
- Annual man days lost due to animal bite: 38 million.
- Annual medicinal (vaccines & other drugs) cost for animal bite treatment: 40 million US dollars approximately.

*An equal number are estimated to be strays.


Rabies in India

- Identified - PCECV (Rabipur)
  - PVBCV* (Verorab, PII, Coonoor & Abhayrab) for use by both IM & ID routes;
  - PDEV (Vaxirab) & HDCV (adsorbed, Rabivax) by IM route only.
- Two doses of vaccine by IM route on day 0, when RIGs are not available.
- Upper limit of 3000 IU fixed for ERIGs & 1500 IU for HRIGs irrespective of body weight of patient.
- Full course of CCV/PDEV for PEP in those who have received NTV in the past.

*Indirab recommended later in 2008
Rabies in South-East Asian Region

Chairperson: Dr. Chris Morrissy, CSIRO Livestock Industries, Australia
Co-Chairperson: Dr. Luningning Villa, Programme Facilitator, ASEAN Plus Three EID Programme
Reported by: Dr. Luningning Villa, Programme Facilitator, ASEAN Plus Three EID Programme

Conclusions:
• Rabies is recognized as a public health problem. Dogs are still the major reservoir of animal bites. Deaths are due to rabies affecting children. Decreasing trend is observed in Philippines and Thailand both in animals and humans. Good practices in some countries. Animal bite treatment centers. Sharing of resources are among local governments. Use of intradermal route
• Laboratory is used for animal and human disease diagnosis. Passage of national anti-rabies law, Disease free zone - initiative (Together with other diseases). Mobile rabies vaccination units, Animal rabies vaccination campaigns, Rabies vaccination posts. Steering committees, Strong government commitment. Intersectoral approach: Donating food to dog pounds. CVNR program: Capture, neutering, vaccinate and release, Community participation. Pre exposure prophylaxis. Restriction of pet travel

Challenges:
• Canine rabies is endemic
• Poor exposure to Post exposure prophylaxis
• Poor compliance to PEP regimen
• Treatment sought with traditional healers
• Low dog vaccination coverage
• Uncooperative/ irresponsible pet owners for dog control/ vaccination
• Myths about rabies / dog bites: ignore bites/ exposure
• Uncontrolled dog population growth
• Trans boundary movement of dogs - poor control of trade and involvement
• Decreasing prevalence of rate of dog vaccination
• Inadequate / low awareness level
• Poor funding support for rabies compared to pandemic flu, H5N1
• Weak institutional linkages
• Absence of policies

Recommendations:
• Mobilize all possible available resources: Involve NGOs and international organizations
• Institutional multi - sectoral rabies advocacy
• Increase role of local governments and community participation
• Increase in post exposure prophylaxis of high risk cases
• Registration/ policies/ legislations
• Direction from government
• Need for an integrated program
• Adopt good practices
Rabies is a disease of the nervous system transmitted by the bite of an infected animal, usually dogs and cats. Every year, around 55,000 people all over the world die from rabies. The disease has no cure. Once symptoms appear, death becomes inevitable. In the Philippines, although rabies is not among its leading causes of morbidity and mortality, rabies is considered a significant public health problem because it is the one of the most acutely fatal infectious diseases, responsible for the death of 200-300 Filipinos annually.

In 2008, 250 human rabies cases were reported in the country. Majority of these cases are males and at least a third of them are less 15 years of age. About 190,000 animal bites were reported to the National Center for Disease Prevention and Control, half of which are children below 15 years old. More than half (55%) of the animal bite victims are males and almost 90% are got the second to dog bites. Access to Post- Exposure Prophylaxis (PEP) has improved in the past years but PEP coverage is still below the national target. Last year, 77% of the Category II and III exposures were given Tissue Culture Vaccines (TCVs) while only 21% of the Category III exposures were given Rabies Immune Globulin (RIG). The three main reasons for human deaths due to rabies are: uncontrolled canine rabies in the country- canine rabies is endemic in the country; failure of poor/indigent animal bite victims to received or complete the recommended Post- Exposure Prophylaxis (PEP) due to high cost of TCVs and RIGs; and belief of some animal bite patients that traditional healers can prevent rabies.

Exposure thru animal bites is still responsible for almost all human rabies in the Philippines. Animal rabies is positive in almost all parts of the country except in some island provinces/municipalities declared or considered candidate for declaration as rabies free zones. Luckily, rabies among animals has been limited to domesticated animals. In 2008, 971 animal rabies cases were reported to the Department of Agriculture- Bureau of Animal Industry (DA-BAI). Ninety eight percent of these are dogs. Dog vaccination coverage is about 20%. According to DA-BAI, the three main reasons for rabies deaths among animals are: poor/low dog vaccination coverage; uncooperative pet owners who refuse to have their dogs vaccinated and irresponsible pet owners who allow their dogs to stray or roam freely.

To control and eventually eliminate rabies in the Philippines a National Rabies Prevention and Control Program is being implemented by a multi-agency/multi-sectoral committee chaired by the Bureau of Animal Industry of the Department of Agriculture.
and vice chaired by the Department of Health. As provided for by Republic Act 9482 or the "Anti-Rabies Act of 2007" the program is a multi-agency effort to control and eliminate Rabies in the country. Among its component activities include: (1) mass vaccination of Dogs; (2) establishment of a central database system for registered and vaccinated Dogs; (3) impounding field control and disposition of unregistered, Stray and unvaccinated Dogs; (4) conduct of information and education campaign on the prevention and control of Rabies; (5) provision on pre-exposure prophylaxis (PrEP) to high risk personnel and Post Exposure Prophylaxis to animal bite victims by trained health workers; (6) provision of free routine immunization or Pre-Exposure Prophylaxis (PrEP) of schoolchildren aged five to fourteen in areas where there is high incidence of rabies as well as the (7) encouragement of the practice of responsible pet ownership.

In the past years, the Department of Health, as part of their Disease Free Zone Initiative and the Department of Agriculture has encouraged and technically assisted local government units of island provinces and municipalities attain a rabies free status. The initiative's priority is islands frequently visited by local and international tourists to promote these areas as rabies-free tourist destination. In 2008, the two Departments jointly declared the island province of Siquijor as the first Rabies Free Island in the country. The declaration of Siquijor as a rabies free island has elicited the interest of local chief executives to implement comprehensive rabies prevention and control program so their island can be declared a rabies free zone.

Considering that almost half of animal bite patients and at least one third of human rabies cases are children below 15 years of age, pre-exposure prophylaxis (PrEP) among school children is being advocated strongly by the government and private sectors. Free PrEP will be provided to school children by the rabies program in highly endemic areas with high incidence of animal bites. Knowing that PEP coverage is still low, both for TCVs and RIG due to the high cost of these commodities, the program is investing on PrEP hoping that this can significantly reduce the cost of PEP in the future by eliminating the need for RIG and reducing TCV requirement to just 2 booster doses. The program is also working with the Philippine Health Insurance Corporation on the inclusion of the management of rabies exposure in their outpatient benefit package.

Other initiatives includes strengthening the partnerships with the private sectors, animal welfare groups, multinationals and other NGOS and POs actively involved in the prevention and control of rabies, exploring the possibility of private-public mix in the provision of PEP, maximizing available resources to increase dog vaccination coverage thru partnerships and lastly, strengthening further the rabies advocacy activities especially during the "March-Rabies Awareness Month" and the "World Rabies Day celebration". The program will be recognizing local government units implementing outstanding rabies prevention and control program in 2010.
Human Rabies Situation in the Philippines

- Rabies is not among the 10 leading causes of morbidity and mortality in the country
- Rabies continues to be a public health problem in the Philippines
  - 200-300 deaths per year
  - One of the most acutely fatal infectious diseases
- 250 Human rabies deaths in 2008
  - Majority are males
  - At least one third of these deaths are children < 15 years of age

National Rabies Prevention and Control Program (NRPCP)

Component Activities:
1. Mass vaccination of Dogs;
2. Establishment of a central database system for registered and vaccinated Dogs;
3. Impounding field control and disposition of unregistered, Stray and unvaccinated Dogs
4. Conduct of information and education campaign on the prevention and control of Rabies;
5. Provision of Pre-Exposure Prophylaxis (PrEP) to high risk personnel and Post Exposure Prophylaxis to animal bite victims by trained health workers;
6. Provision of free routine immunization or Pre-Exposure Prophylaxis (PrEP) of schoolchildren aged five to fourteen in areas where there is high incidence of rabies;
7. Encouragement of the practice of responsible pet ownership.
In the past 10 year rabies situation in Thailand has been decreasing both in animals and human. From 63,389,730 human population, number of human death from rabies decreased from 57 (0.94 per 100,000 population) in 1998 to 9 (0.027 per 100,000 population) in 2008. Number of animal bites or exposure per year varies from 300,000 to 400,000 and estimate immunoglobulin used varies from 17,000 to 25,000. Human vaccines used in Thailand are PCEC, HDCV (Sanofi) and PVRV (Biogentech) and only Equine Rabies Immunoglobulin (ERIG) produced from Queen Saovapa Memorial Institute (QSMI) is used. Dogs are the main reservoir of 91-95% rabies positive from submitted cases. From about 7,000,000 dog population which 10% is stray, positive cases from submitted animals decreased from 28.61% in 1998 to 20.18% in 2008. Currently 6 animal rabies vaccines are available for animal use which are Rabisin (Merial), Rabigen mono (Vir), Rabvac (Fort Dodge), Rabdomun (Intervet Shering Plough, Rabguard and Rakharab (Pfizer). Percentage of vaccination coverage in dogs and other reservoir animals varies from 55-65% due to dynamic of dogs. Three main reasons for human rabies deaths are bitten by unvaccinated owned dogs, ignorance of dog bite wound and misunderstanding or misbelieve about rabies such as rabies occurs in summer only and found in dog only. Three main reasons for animal rabies deaths are insufficient vaccination coverage such as unvaccinated owned dogs, stray feeding and unrestrained dogs and stray. Currently rabies free area establishment, integrated rabies control to Sub-district level, community participation, dog vaccination and dog bite prevention campaign, post-exposure for all risk persons and law enforcement have been launched to eliminate rabies. Public awareness to high risk groups is one of the most important strategies.

Rabies in Thailand number of human deaths rabies vaccine in human and animals current control strategies
1. Source: Department of Provincial Administration, Ministry of Interior
2. Source: Bureau Epidemiology, Ministry of Public Health
3. Source: Department of Disease Control, Ministry Public Health
4. Source: Bureau of Disease Control and Veterinary Services, Ministry of Agriculture and Cooperatives
About Human Rabies

Human death per 100000 population

Human death per 100000

0.000 0.005 0.010 0.015 0.020 0.025 0.030 0.035 0.040 0.045

2003 2004 2005 2006 2007 2008

Year

0.029 0.031 0.032 0.040 0.027 0.014

Source Bureau Epidemiology Ministry of Public Health

Department of Livestock Development

Today ...Rabies Control in Thailand

- Rabies Free Area Establishment
- Integrated Rabies Control to Sub-district level
- Community participation
- Dog vaccination and dog bite prevention campaign
- Post-exposure for all risk person
- Registration/ Law enforcement

Department of Livestock Development
Rabies situation in Vietnam, 2008

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Rabies is considered as a neglected infectious disease and often paid less attention. With a crucial transmission method from animal (e.g. dog, cat) to human and case fatality rate of 100%, rabies is being a major public health problem not only in developing countries, especially in ASIA and AFRICA, but also in developed countries. Therefore, the effective combination between prevention and control measures aimed to eliminate the rabies from both animal and human health system are essential requirements.

In Vietnam, rabies vaccination rate was 378.3/100.000 population, and the mortality rate of rabies was 0.107/100.000 in 2008. Dogs and cats are main rabies reservoir. Among those who received post rabies exposure treatment, 86.6% was exposure through the dog bites and 8.0 % through cat bites. There are a number of rabies vaccines available for human use in Vietnam, namely Verorab, Sanofi-Pasteur; Rabivac; Rabipur. Rabies immunoglobulin such as Favirab from Sanofi Pasteur and Vaccine Company No.2 Nha Trang were also available. Besides, rabies vaccines were also available for animal use, namely Rabies (Median) and Rabisin (Navetco). Nationwide rabies vaccination coverage in dogs/cats was approximately 50%. Three main reasons for human rabies deaths: No vaccination, delay of vaccination, and severe wound. Three main reasons for animal rabies deaths were no vaccination, incorrect way of vaccination and poor dog management. Activities for prevention and control of rabies in humans and animals are strengthening the rabies surveillance system and post-exposure treatment sites; training health staff and setting up the network of collaborators; carrying out information, education and communication activities; and management of dog population in the high risk areas.

Source of data: National Program for Rabies Prevention and Control
RABIES VACCINATION AND DEATH RATE PER 100,000 POPULATION, 1992-2008

VACCINATION RATE PER 100,000 POPULATION BY REGION
Australia has a population of approximately twenty two million people and, in spite of large pet and feral cat and dog populations, is free of rabies. Australia has the advantage of being an island and maintains freedom by border controls and surveillance. There have been three human cases of rabies in Australia in 1867, 1987 and 1990. Only the cases in 1987 and 1990 were confirmed and both these cases were imported and had long incubation periods. The history of these cases will be presented in the presentation, including the case assessment and presentation of additional sequencing information recently made available from one episode.

Australia uses vaccine for pre-exposure prophylaxis for rabies: Mérieux Inactivated Rabies Vaccine - Sanofi Pasteur Pty Ltd and Rabipur Inactivated Rabies Virus Vaccine - CSL Biotherapies/Novartis Vaccines. Pre-exposure prophylaxis with rabies vaccine is recommended for:

People in Australia liable to receive bites or scratches from bats (this includes bat handlers, veterinarians, wildlife officers and others who come into direct contact with bats),

Expatriates and travelers who will be spending prolonged periods (i.e. more than a month) in rabies-endemic areas. (NB. This time interval, of more than a month, is arbitrary, and rabies has occurred in travelers following shorter periods of travel),

People working with mammals in rabies-endemic areas, and

Research laboratory personnel working with live Lyssaviruses.

Both human rabies immunoglobulin (HRIG), Imogam Rabies - Sanofi Pasteur Pty Ltd, and rabies vaccine are available for post-exposure treatment.

AAHL is the Australian national reference laboratory for rabies and Australian bat Lyssavirus. The diagnostic capability includes the fluorescence antibody test (FAT), polymerase chain reaction (PCR) and sequencing, virus isolation in Neuro 2a and MNA
cells and suckling mice and immunohistochemistry for agent detection and identification and the rapid fluorescent focus inhibition (RFFIT) test and fluorescent antibody virus neutralization (FAVN) test (virus neutralization assays) and ELISA for serology to confirm vaccine response in humans and in animals for certification in pet travel schemes. AAHL has recently conducted trials of a rapid test for rabies, the BioNote One Step rabies antigen test kit, for detection of ABLV and will provide some data on test performance.

Potential sources of rabies entering Australia are illegal entry of rabid dogs or other animals, or deliberate release (Bioterrorism). To prevent Rabies virus entering Australia provides pre-border surveillance support for Papua New Guinea and Indonesia, laboratory support (equipment, reagents) and training for laboratory and field staff, Australia has a rabies emergency plan, The Australian Veterinary Emergency Plan (Ausvetplan), which is a reference resource for veterinary personnel in the event of a suspected outbreak,

Local government requires compulsory registration of all dogs and in most states cats, and undertakes stray dog control activities,

Training courses are conducted for animal health personnel:
Animal Health Australia / AAHL: Courses for government veterinarians in exotic disease recognition
Animal Health Australia / State veterinary departments: weekend refresher courses for private veterinarians in exotic disease recognition and control
Rabies represents a significant cost to the Bhutanese community due to the cost of control measures, loss of livestock, and human life. The cost of post exposure rabies treatment of humans that have been bitten by dogs has been at US$ 0.070 million annually. Dogs are the main reservoir hosts for rabies in Bhutan. The government of Bhutan has assigned high priority to rabies control and is in the process of drawing up a major control strategy designed to reduce the incidence of disease.

Various control measures were tried to effectively control rabies in Bhutan. Nationwide elimination of dogs as a means to control rabies was introduced in 1980s. Following this ad-hoc vaccination and sterilization of dogs was initiated to control rabies in Bhutan. The revamped rabies control programme was started from 2004 onwards. As a result of initiating various control strategies now the majority of the outbreaks were reported in districts adjacent to the southern border of the country only. The spatial distribution of rabies outbreaks in interior districts was consistent with the pattern of seasonal migratory routes taken by domestic animal species (mainly cattle).

Rabies control documents was reviewed and amended from time to time. Some of the recent modifications based on WHO & WSPA expert recommendations are a) control of habitats; ii) legislative measures and iii) animal birth control measures. Department of Livestock is carrying out advocacy campaign on the control of dog habitats to the general public through mass media, public meetings and sensitization meetings of the stakeholders. Besides, Department is also closely working with Municipal Corporation on the management of solid wastes in major cities. Rabies Control Regulations was prepared with the support of international expert fielded through the WHO supported Project on Control of Rabies in Bhutan in year 2007. The regulations outlines the roles of a responsible dog ownership, role of municipal corporation and general public in control of dog habitats and management of stray dogs. Since the animal birth control (ABC) is a proven technique to control the dog population and rabies, Department of Livestock under Ministry of Agriculture in collaboration with Humane Society International (HSI) is now carrying out a nationwide Capture, Neuter, Vaccinate and Release (CNVR) Programme. The techniques adopted in the current CNVR programme is technically and scientifically accepted by international scientific communities and humane societies. The success of the programme is monitored and evaluated using a wild life technique called "Capture-Mark-Recapture" Technique. This technique allow us to evaluate the CNVR programme as well as to estimate the approximate free roaming dog population in the areas. This joint
programme will be seriously carried out for a period of three years and will be continued if felt necessary.

There is also comprehensive policies on management of rabies cases as well as on the response to a rabies outbreak in the field. Religious aversions to elimination of reservoir hosts i.e. stray dogs even during the outbreak was a major problem faced in the control of rabies in some parts of Bhutan. Such an issue demands sound policies and adequate public education which is currently being pursued in Bhutan.
Rabies in Mongolia

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Mongolia with an area of 1,564.1 thousands km2 includes a total of 21 provinces, 365 districts and 3 cities. In the most territories of Mongolia, it exists the high active rabies natural foci. Compiling data from 34 reports of rabies human cases and 153 soums of 18 provinces and 1 district of the capital city for animal cases were recorded during 1996-2008.

Most of animal cases were cattle’s cases (48.4%). 21.7% of total animal cases were occurred in the territory of Khuvsgul province, 9.3-17.3%- in western provinces such as Gobi-Altai, Uvs, Khovd and Zavkhan provinces 70.8% of all cases occurred during the season from March to June.

During 1996-2008, a total of 1,535 cases of animal rabies were recorded in Mongolia. 82% were livestock cases, 15.3% were dog cases. Children aged 0-9 dominated by 41.2%- in the age group while male 58.8% (20) and female 41.2% (14). All patients were not treated by immunoglobulin in which about 53% (18) were not involved in vaccination. During last 10 years, 162 people were bitten by rabies suspected animals in territories of 78 soums of 16 provinces. Approximately 49% of all bitten people were bitten by dogs, 35%- by wolves, 2.0%- by foxes, 14%- by livestock 25% of all rabies suspected animal cases were confirmed by laboratory. In 30 provinces and 2 cities of the country, 2,337 wolves and 45,836 stray dogs were perished.

Dogs, wolves and foxes play the main role in the rabies distribution in Mongolia. Livestock rabies cases become an indication of rabies epizootic intensity in Mongolia. Rabies foci are more intensive in central and western parts of Mongolia. 70.8% of all livestock cases recorded in months from March to June and cattle dominate among infected livestock. The highest number of human cases was often occurred in July of the year. The common laboratory test using serology rapid tests produced in Korea is conducted to confirm the human rabies cases. A total of 32 samples of cattle, foxes, wolves, camels and dogs from Gobi Altai, Zavkhan, Khentii, Ulaanbaatar tested for rabies antigen were turned to positive.

Therefore, in order to halt the rabies spreading, a series of training course for rabies control and prevention were implemented nationwide and the country also set up rabies control initiatives (1) to improve laboratory bio-safety, (2) to increase a number of people vaccinated, (3) to improve strategy to deal with actions between veterinaries and hospitals.
Human cases

Epizootology
SESSION 2. UPDATE PRACTICES IN HUMAN AND ANIMAL RABIES SURVEILLANCE, PREVENTION AND CONTROL

UPDATE ON HUMAN RABIES PREVENTION:

Chairperson: S.N. Madhusudana, NIMHANS, Bangalore  
Co-chair person: Dr.B.Quiambao, RITM, Alabang, Philippines  
Reported by: Dr. B.Quiambao, RITM, Alabang, Philippines

This session tackled updates on rabies vaccination, pre-exposure prophylaxis and lessons learned from the experience of other countries.

The importance of pre-exposure prophylaxis as a strategy for rabies prevention, especially among school children, was emphasized in 3 papers. A study from Thailand has shown that rabies vaccine can be safely given with Japanese encephalitis vaccine without any significant effect on the development of antibody titers. Concomitant administration of rabies vaccine with other childhood vaccines can assist in the integration of rabies in the national immunization program for children. Follow-up booster studies on previously immunized children showed adequate anamnestic response regardless of whether the 2 booster doses were given after 1, 3 or 5 yrs after the primary vaccination. These studies lend support to the recommendation of giving pre-exposure prophylaxis to children. In fact, in the Philippines, rabies pre-exposure prophylaxis is already mandated by the "Anti-rabies act of 2007". Data from this country shows that pre-exposure vaccination of school children is acceptable to the general population.

An interesting meta analysis of 21 published studies to assess the relationship between antigenicity and immunogenicity of rabies vaccines was presented. The study found that, vaccines with higher antigenic value did not result in significantly higher antibody titers. A recommendation to specify the potency of the ID dose & a common ID schedule was made for universal usage.

Data on the safety and efficacy of the 4-site ID booster routinely used in Thailand was presented. The regimen was found to be effective and had the advantage of reducing the number of clinic visits and the consequent costs of transportation and working time lost. Data on the use of this regimen has been submitted to the WHO for evaluation. Preliminary data of a new shortened post-exposure prophylactic regimen using 4 ID doses on days 0, 3, 7 showed good antibody response, providing another promising regimen to consider. The importance of wound care and avoidance/postponement of suturing was emphasized. Washing the wound can decrease the risk of rabies by as much as 40%.

Finally, lessons learned in the Philippines from the shift of nervous tissue vaccine (NTV) to cell culture vaccines were presented. The change is not easy and will require commitment, logistic support and a national rabies control program. The implementation of the intradermal regimen of rabies vaccination can help developing countries still using NTC in making this shift.
New Developments and Controversies in Rabies

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The volume of knowledge of rabies gained during the last two decades is considerable. We understand much of the epidemiology, pathophysiology and techniques of prevention. We have the tools to implement much of what is needed but the problem of endemic canine rabies remains. Most developed countries, and some that are still struggling, have found a way to control canine rabies. It was done by education of the public and health care professions, legislation by their national government and enforcement of strict dog control laws by the police and municipal officers. How this can be promoted and carried out in the rest of Asia remains our largest challenge. An abbreviation of the "gold standard" rabies post-exposure regimen (PEP) by the US-CDC has now been released. Further shorter schedules are undergoing studies in Asia. The Thai Red Cross intradermal PEP schedule is expanding its range because it saves funds as well as vaccine. Several publications have shown that even properly performed PEP may not be 100% effective, thus further emphasizing the need for meticulously carried out PEP and documenting it in detail. Several studies by Hemachudha et al have cleared up the enigmatic nature of furious and paralytic clinical presentations. They are due to different host responses and not viral variations. The complete recovery of a 15 year old American girl who had no PEP at all created hope that rabies may, after all, be treatable. Repeat efforts on 12 patients at major medical centers failed and shattered our hope for the time being.
Assessing the relationship between antigenicity and immunogenicity of human rabies vaccines when administered by intradermal route: Results of a meta-analysis

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The data of 21 published studies from four countries conducted over a period of 23 years (1986 - 2009) was used for meta-analysis. The vaccines studied were purified chick embryo cell vaccine (Rabipur, India & Germany), purified vero cell rabies vaccine (Verorab, France; Indirab, India) & human diploid cell vaccine (MIRV, France). The antigenicity/potency of these vaccines varied from 0.32 to 2.32 IU per intradermal dose of 0.1ml per site, except in one study which was 0.2ml per ID site. The vaccines were administered to 1098 subjects using five different ID regimens. The immunogenicity was measured by assays of rabies virus neutralizing antibody (RVNA) titres using rapid fluorescent focus inhibition test (RFFIT) [16studies] and mouse neutralizing test (MNT) [5 studies].

The statistical analysis of the data was done by computation of combined geometric mean titres (GMT's) and Karl Pearson's correlation coefficient of RVNA on days 14 & day 90. It was revealed that, an higher antigenicity of rabies vaccine viz. potency of > 0.7 IU per ID site of 0.1ml dose did not produce significantly higher immunogenicity/ RVNA response in the vaccinees on day 14 (r=0.290, p>0.203) and day 90 (r=-0.099, p>0.668). In conclusion, there was no significant linear relationship between antigenicity/potency and immunogenicity/ RVNA response of rabies vaccines when administered by intradermal route.

[Presenter: Dr H S Ravish][Corresponding author: M. K. Sudarshan @ gmail.com].
Providing booster in one day using 4-site intradermal vaccination

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Backgrounds: Previously rabies vaccinated individuals need only booster vaccination when re-exposure occurs. Rabies immune globulin (RIG), the biological product which is scarce and expensive, is not required in those patients. An earlier study demonstrated that a single visit with patient receiving four-site intradermal (ID) injections at deltoids and thighs using 0.1mL of tissue culture rabies vaccine administered on day 0, required only one clinic visit. It induced significantly higher titers of rabies neutralizing antibody (RNAb) than the standard two-booster dose on days 0 and 3. The four-site ID booster vaccination is being routinely used in the Queen Saovabha Memorial Institute since 1998.

Methods: We carried out a retrospective study of all patients who received the four-site ID boosters at QSMI. The out-patient records were reviewed from 1998 to 2008.

Results: A total of 5,116 patients received the four-site ID regimen and 3,335 of this group (65.2%) incurred severe potential rabies exposures (WHO category III) and 253 patients (4.9%) were bitten by laboratory confirmed rabid animals. The youngest was 2 year-old and the oldest was 83 year-old. There were 2,453 male patients (48.1%). The longest period since primary rabies vaccination was 25 years. None had serious adverse reactions and there were no reports of human rabies deaths among this group.

Conclusions: The four-site ID booster schedule is effective, saves transportation expenses as well as loss of working time and may reduce non compliance. This can be an advantage for patients living in rural regions and for international travelers. The regimen was previously presented to the WHO expert committee with a request for approval. This request is now under consideration.
Rabies is a fatal but vaccine preventable infectious disease that continues to plague many countries in the world.

More than a hundred years have passed since Louis Pasteur and his colleagues successfully immunized a 9 year old boy with a crude rabies vaccine based on attenuated virus in desiccated nerve tissue. Since then, many advances in rabies prevention have occurred. Nerve tissue vaccines (NTV), derived from the brains of sheep, goat or suckling mice, have been replaced by tissue culture vaccines (TCV), eliminating the encephalitic reactions associated with NTV and providing improved immunogenicity and efficacy.

The Philippines is one of the first Asian countries to shift from NTV to TCV for rabies prevention. The implementation of this shift was gradual, with the establishment of specialized centers providing rabies post-exposure prophylaxis (termed animal bite treatment center or ABTC) in existing hospitals or health centers. Both the intramuscular and intradermal regimens were utilized in the beginning. When more and more people began seeking treatment at the ABTCs, it was decided to implement the intradermal regimen nationwide. Currently, there are more than 250 government and about 100 private bite centers in the country, providing post-exposure prophylaxis to animal bite victims.

Several lessons were learned from this experience: (1) there is a need for a multi-agency National Rabies Control Program geared towards the prevention and control of both human and animal rabies; (2) national standard guidelines on the management of animal bite victims need to be in place; (3) the benefits of the intradermal regimen can be maximized if post-exposure prophylaxis is provided by specialized treatment centers where staff are trained on the administration of vaccine and rabies immunoglobulin and in the management of adverse reactions; (4) a consistent supply of safe and effective rabies vaccines and immunoglobulin should be assured, with the Department of Health most likely providing some of the doses and the local government unit contributing the rest; (5) coordination with local government units is essential in ensuring sustainability of the rabies control program.

The shift from NTV to TCV is fraught with many challenges. But the benefits far outweigh the difficulties involved.
Pre-exposure children and population at risk: When should it be implemented?

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Pre-Exposure Prophylaxis (PrEP) is the administration of rabies vaccination before a person is exposed to potentially rabid animals. PrEP does not eliminate the need for medical evaluation and management of rabies exposure. It simplifies the management for previously vaccinated persons by eliminating the need for rabies immune globulin and reducing the required number of vaccine doses to two booster doses thereby reducing significantly the cost of Post-Exposure prophylaxis (PEP). PrEP simplifies the Post-Exposure prophylaxis (PEP) of previously vaccinated persons by priming the immune response, enabling a rapid anamnestic response to post-exposure booster vaccination. PrEP can also provide some protection for persons at risk for unrecognized or unapparent exposures to rabies.

PrEP is indicated for persons whose occupation, travel or recreational activities place them at higher risk of exposure to rabies. Veterinarians, animal handlers, pet owners, staff in the rabies laboratory, hospitals handling rabies patients, dog catchers, animal vaccinators and others at risks are recommended to have the necessary PrEP. International travelers are likewise recommended to have PrEP if they are likely to come in contact with animals in countries where animal rabies is enzootic and immediate access to appropriate PEP may not be available. However, routine PrEP for the general population is not recommended.

In the Philippines, where almost half of animal bite patients and at least one third of human rabies cases are children below 15 years of age, children between five to fourteen years old residing in highly endemic areas are also provided with free PrEP. This is provided for by Republic Act 9482 or the "Anti-Rabies Act of 2007".

In rabies endemic countries where access to PEP is difficult, PEP coverage and compliance is low and cost of anti-rabies vaccine and immune globulin is prohibitive, routine PrEP for high risk individuals should always be available.
Immunogenicity, booster response and safety of purified chick embryo cell rabies vaccine administered intramuscularly or intradermally to 12- to 18-month-old Thai children, concomitantly with Japanese encephalitis vaccine

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Background: Combining JE and rabies vaccination would give the advantage of introducing rabies vaccination, when toddlers start being at risk. This study evaluated the immunogenicity, immunologic memory, and safety of purified chick embryo cell rabies vaccine (PCECV) administered in pre-exposure regimens concomitantly with JEV to 12- to 18-month-old Thai children.

Methods: Two hundred healthy children aged 12 to 18 months were randomized into 5 groups in a 2:2:2:2:1 ratio - group 1: full-IM (n = 44): vaccination with 1.0 mL PCECV intramuscularly (IM) on D0, D7, and D28; group 2: half-IM (n = 45): vaccination with 0.5 mL PCECV IM on D0, D7, and D28; group 3: 3-ID (n = 44): vaccination with 0.1 mL PCECV intradermally (ID) on D0, D7, and D28; group 4: 2-ID (n = 44): vaccination with 0.1 mL PCECV ID on D0 and D28. All subjects received JE vaccination with 0.25 mL JEV subcutaneously on D0 and D7 concomitantly (groups 1-4) or without PCECV (group 5: JEV only, n = 23). All groups received booster doses of JEV (groups 1-5) and rabies vaccine (groups 1-4) at 1 year after the first dose. Blood was drawn from each subject before vaccination, on D49, Y1 (before booster), and on 7 and 28 days after booster for rabies and JE neutralizing antibody (RVNA and JEVNA). RVNA were also determined at 2 and 3 years after primary vaccination.

Results: While higher RVNA concentrations were seen after both IM regimens than after the ID regimens, all four rabies immunization schedules resulted in adequate immune responses at D49. One year after primary immunization all children vaccinated with the IM schedules maintained adequate RVNA concentrations (>0.5 IU/mL), while 97% and 61% of children vaccinated with the 3-ID and 2-ID schedules had adequate values, respectively. After booster, all children demonstrated an anamnestic immune response regardless of the pre-booster antibody concentration. All children in both the IM and the 3-ID groups had adequate immune responses by Y1+7 days, Y1+28 days, Y2, and
Y3. In the 2-ID group, the rate of adequate RVNA concentrations decreased to 93% and 80% at Y2 and Y3, respectively. All children had JE seroconversion (JEVNA >1:10) at D49 after primary JE immunization and had adequate immunity at 1-year follow-up without significant differences among the groups. No significant immediate adverse reactions occurred after vaccinations and both PCECV and JEV were well tolerated.

**Conclusion:** PCECV and JEV administered concomitantly are immunogenic and safe in toddlers. Both IM and the 3-ID regimens demonstrate long-lasting immunogenicity, persistence of immunologic memory, good safety and convenience of administration.
Rabies Pre-exposure Prophylaxis in Children: Anamnestic immune response to PCECV booster doses up to 5 years after primary vaccination

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Intradermal (ID) rabies pre-exposure immunization with PCECV has been demonstrated to be safe and immunogenic in schoolchildren. In this follow-up part of a randomized, open-label, phase II clinical trial, simulated post-exposure booster doses of 0.1 mL PCECV (Rabipur®) were administered on days 0 and 3 intradermally to 703 schoolchildren, one, three or five years after a primary vaccination series of two or three ID doses of 0.1 mL PCECV. The objective of the study was to investigate the anamnestic immune response in terms of post-booster rabies virus neutralization antibody concentrations, as measured by rapid fluorescent focus inhibition test. The clinical trial was done following GCP guidelines under permission of the Human Research Committee, Ministry of Health, Thailand.

After two booster doses, an anamnestic response of about 30-fold increasing RVNA concentrations was demonstrated within 14 days. All children developed adequate RVNA concentrations above 0.5 IU/mL, when booster doses were given one, three, or five years after primary vaccination.

While a difference in overall immune response was demonstrated, whether two or three primary doses were given, the ratio of post-/pre-booster increase was similar regardless of the timing of the booster doses, one, three, or five years after primary vaccination.

No vaccine related serious adverse events were seen in any of the 703 vaccinees.

Rabies ID pre-exposure immunization with PCECV is safe and immunogenic in schoolchildren and anamnestic responses to two booster doses were found to be adequate five years after primary vaccination.
Best practice in laboratory diagnosis and surveillance of rabies

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Rabies continues to be a significant health problem in most developing countries of Asia and Africa. It is a zoonoses and more than 95% of human deaths are due to bites from infected dogs. Laboratory diagnosis of rabies plays an important role in confirming rabies in the suspect animal, in ante-mortem diagnosis of atypical paralytic rabies and in epidemiological surveillance of rabies. The post mortem diagnosis is 100% confirmatory by the currently available techniques. The earliest technique developed was demonstration of Negri bodies in the brain smears by Seller's staining. This technique is only 60% sensitive and negative tests does not rule out rabies. Presently the fluorescent antibody technique (FAT) is the gold standard which is almost 100% sensitive and specific in an experienced laboratory. Other techniques that can be employed include an ELISA which is called rapid rabies enzyme immuno diagnosis (RREID) and recently developed direct rapid immuno histochemistry (dRIT). Molecular techniques are not routinely performed for rabies diagnosis post mortem.

Virus isolation in mice or cell lines is required for confirmation and also for molecular and genetic characterization. Ante-mortem diagnosis of rabies can be done by doing a FAT on corneal smear and frozen section skin biopsy. It can also be done by demonstration of viral RNA by RT-PCR or a Real Time PCR using saliva samples. Generally, rabies nucleoprotein targeted primers are used to amplify a specific segment of the N gene and this is detected by gel electrophoresis. For further characterization of the strains circulating in geographical location G protein specific primers are used. Based on the genetic characterization, 7 genotypes have been identified. Genotype I is prevalent in most parts of the world and all the strains isolated from Asia belong to Genotype I. Several studies have been done for the molecular characterization both in India and abroad. Distinct differences in the geographic distribution of the viruses have been demonstrated based both on N and G gene of the virus.

Presence of rabies antibodies in CSF is diagnostic of rabies. Apart from this...
detection of rabies antibodies is also done for monitoring sero-conversion in patients who have taken post-exposure vaccination. Currently two techniques are recommended for estimating rabies virus neutralizing antibody titers. These include Rapid Fluorescent Focus Inhibition Test (RFFIT) and Fluorescent Antibody Virus Neutralization Test (FAVN). Though there are commercially available ELISA kits for estimating rabies antibodies they are not recommended by WHO as these do not detect neutralizing antibodies.

Virus isolation by Rapid Tissue Culture Infection Test (RTCT) using cell lines such as Murine Neuroblastoma (N2a), CER, BSR or BHK 21 cells may be required in cases of FAT negative specimens. Antigen detection by FAT may be negative in cases where animal is killed early in the disease process. Virus isolation is also required for genetic characterization of the virus strains prevalent in a particular geographical area.

Good laboratory practices are very important in laboratory diagnosis of rabies. This could be with the use of good quality reagents, good techniques and correct interpretation. For quantification of rabies neutralizing antibodies, the second international preparation of rabies immunoglobulin (RIG) having a potency of 30 IU/mL. This can be obtained from National Institute of Biological Standardization, UK. As this preparation is expensive and of limited supply, it is advisable for laboratories to calibrate their own in-house reference serums against the international preparation.

Periodic assessment of the laboratory by an external quality control authority is necessary for instilling confidence. Inter laboratory networking is also essential for periodic cross evaluation of the results. Periodic training of the laboratory personnel in a reference laboratory is essential for upgrading the techniques and institute newer techniques that may be developed.
UPDATE ON ANIMAL RABIES CONTROL

Chair person: Dr. Ong Bee Lee WHO / WPRO
Co-Chair person: Ms Stella Marie D. Lapiz, DVM, Provincial Veterinarian,
Provincial Government of Bohol
Report by: Ms Stella Marie D. Lapiz

Conclusions:

- Paradigm shift: Focus from human rabies PEP to canine rabies elimination.
- Need to achieve high vaccination coverage to reach the goal of rabies elimination within the Gates foundation project areas.

Challenges:

- Sustaining efficient conduct of mass vaccination by government carried out for free / for free but collect registration fee.
- Animal Birth Control needs to be explored.
- Stronger political will and commitment for logistic and legislative support.

Recommendations:

- Explore the use of many rapid tests available for human rabies diagnosis.
- Studies to support the gaps in knowledge of rabies situation in Mongolia especially on the reservoir of wildlife rabies.
- Paradigm shift from human PEP to canine rabies control.
- In Countries with limited resources and funding, need to rethink on how best to deliver canine mass vaccination campaign in a sustainable manner.
- Need to find sustainable, cost effective model for delivery of dog vaccination, dog population management especially as a community model.
- Explore the good models and practices shared by different countries such as Philippines, Sri Lanka and the NGO's such as WSPA.
- Encourage countries to get involved with World Rabies Day to educate and raise awareness to public, decision makers and others.
- Continue to use media to promote the awareness of rabies elimination and strong political support.
- Promote active Government, private and community collaboration in implementing animal rabies control.
- The participants requested WHO, the ASEAN + 3 countries secretariat, ARC, Aus AID & other partners to assist Indonesia & the provincial government of Bali to eliminate rabies from Bali according to most current internationally recognized dog rabies control & population management techniques.
Dogs are clearly a species of interest when considering rabies control, with approximately 98% of all human cases transmitted via domestic dogs. The global dog population is estimated to be one tenth of the human population (i.e. around 600 million). This impressive population size and the ubiquitous spread of dogs across human societies make dogs an essential consideration for every nation considering rabies control.

Considering the importance of dogs as a vector for rabies, it is not surprising that mass vaccination of dogs has proven to be highly effective in controlling this disease. For example in Mexico, after 5 years of a nationwide dog vaccination campaign, the number of human rabies deaths was reduced from 60 per year to less than 20. Subsequently, human cases have been almost eliminated throughout the country (ARC).

Although vaccination alone is effective, providing additional dog population management interventions may improve rabies control by reducing population turnover and hence prolonging vaccination coverage, reducing the number of unowned stray dogs which may be more difficult to access for vaccination and increasing the 'value' of individual dogs so that owners may make more effort to get their dog vaccinated.

Several challenges exist for implementing efficient dog vaccination and population management, including accessing a sufficient proportion of the dog population, ensuring the sustainability of interventions and the use of tools that are suitable for the location and resources available. These challenges and potential solutions will be discussed in the presentation.
Running a Rabies Control and Eradication Program is a difficult task to handle. In fact, it is a mission impossible for the government to pursue alone, as what had been observed for the past years. Not only is the task expensive but also very tediously demanding. We have to change and modify the traditional way of raising dogs and other animals in order to control the invisible dreaded disease that can possibly thrive in them, Rabies.

With the above scenario, it is not hard to imagine that Government could not hire as many people that could possibly implement the lofty goal of eradicating Rabies. Even the best laws and legislation could mean nothing without the complementary enforcement. It is for this essence that community mobilization becomes indispensable. We have to get the people to work for their own advantage.

The Bohol experience is a proof enough that the approach is working. Remarkable results were already apparent since its application two years ago. From being third among the provinces in the Philippines in terms of human rabies fatalities, we have reduced the cases by fifty percent (50%) in the first year. Since the start of 2009 until today, no confirmed human and canine rabies incidence has been reported based on the comprehensive monitoring.

The community-based rabies project has yet to be fully implemented. As of this period, the Bohol Rabies Prevention and Eradication Council (BRPEC) have done the following vital interventions: Institutionalization of the 1,109 "BRB" or the Bantay Rabies sa Barangay (Community Rabies Watchers) that implements the program at the grassroots level; Community based rabies disease prevention and responsible pet ownership advocacy campaign; Technical and operational capacitation of all the BRB’S; Establishment of Barangay Rabies Data Base; Developed and implement a community reporting and monitoring system; Integration of rabies awareness and responsible pet ownership in elementary school curriculum throughout the entire province; Generation of external support for its program financing; and Sharing of experience for other provinces/countries to replicate.

At present, we are working towards the attainment of seventy percent (70%) canine rabies vaccination to achieve herd immunity. Thru the community effort, the goal is almost at hand.
Introduction

Dog population in the island has been estimated around 2.5 million on the basis of dog ecology survey conducted in 1980s which revealed that dog: human ratio was 1:8 (WHO 1988). Another study which was conducted in two rural areas situated 45 km northeast of Colombo, Meerigama has revealed that, inhabitants per dog was 4.6. Density of dog population is 108 per square kilometer. About 19.4% are ownerless dogs. Further, among the owned dogs older than 3 months 39.6% were confined and 60.4% is free roaming (Matter et al. 2000). As human population density is also high in many areas dog human interaction can lead to an unprecedented number of dog bites and increase risk of acquiring deadly rabies thorough dog bites. In the year 2008, an estimated number of 174,000 animal bite victims were initiated with rabies post exposure treatments (PET) at government hospitals which consumed 344,555 vials of Human anti rabies vaccines.

<table>
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<td>274000</td>
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Estimated Number of animal bite patients initiated with rabies PET at government hospitals. (Source: Public Health veterinary services, Sri lanka)

Main control strategies are mass dog vaccination which include both stray and owned dogs, and population control of dogs which include surgical and chemical sterilization of both stray and owned dogs.

Dog vaccination, first launched in 1975, is carried out annually, free of charge, by certified vaccinators in the district rabies control units. During these vaccination campaigns, vaccination of owned dog is carried out at pre arranged temporary vaccination posts while stray dog vaccination is carried out using a special device called 'Auto Plunger'. The owner is given a vaccination certificate and dog collar which is helpful to identify unvaccinated dogs during free roaming dog vaccination.

Present situation

Due to the limited facilities for animal rabies surveillance dog rabies incidence is largely undetermined. On the basis of rabies diagnosis at three laboratories in Colombo,
Galle and Peradeniya, nearly 90% of rabies diagnosed in animals was among dogs.

Animal Rabies Positives 2007/2008 (Source: Medical Research institute, Sri Lanka)

Animal rabies vaccine available in Sri Lanka, are killed vaccines. Over 90% dog rabies vaccination carried out by government program at no cost to the owners. Veterinarian vaccinate small proportion of dogs at a cost around 5 US$ which is paid by the owner.

Elimination of stray dogs had been carried out since 1975 and abandoned in 2005 and this was replaced by surgical and chemical animal birth control (ABC) methods.

Percentage of mass rabies vaccination of dogs has increases from 3.2% in 1977 to 49% in 2008. Dog elimination rate always was below 10%. Rate of New strategies of Animal birth control were 4% with chemical and 5% with surgical method.

Figure 1 Corelation of Human rabies deaths against Dog vaccination.
(Source: Public Health veterinary services, Sri lanka)
It has been observed that the correlations between human rabies deaths rate and dog vaccination rate (-0.589; p<0.01) (Figure 1) and human rabies deaths rate and dog elimination rate (-0.589; p<0.01) for the period of 1975 to 2006 were negative and statistically significant (Kumarapeli & Awerbuch-Friedlander 2009).

**Discussion**

Tremendous decrease of human rabies has been revealed after establishment of dog vaccination and removal since 1975. In additions Zero incidence of human rabies has been achieved in Puttlum district in 2007 with special interventions such as supplementary oral rabies vaccination to reach high coverage of 77.7%.

![Figure 2: Dog Vaccination coverage by district. (Source: Public Health veterinary services, Sri lanka)](source)

Vaccination coverage of 49% of dogs is not sufficient to eliminate dog rabies and gradual increase of vaccination coverage has led to reduce human rabies (Kumarapeli & Awerbuch-Friedlander 2009). However coverage vary among districts from 0.0% in Kilinochchi & Mullathiv districts to 108% in Polonnruwa (figure 2) where zero reporting of human rabies was recorded last 4 years.

Sri Lanka also has well established public health infrastructure and necessary expertise to develop rabies eradication program. Further as that Sri Lanka being an island, National rabies control programme can be launched without rely on neighbours and once eradicated it is very easy to prevent re-entry of rabies into the country. Therefore mass dog vaccinations should be the main dog rabies control strategy while animal birth control needs to be explored for optimal coverage need for rabies elimination without disturbing ecology of animals living in urban settings. Promotion of Responsible dog ownership, Updating and effective implementation of legislation, advocacy on isolation of rabies suspected dogs and other control measures also need to be strengthen to achieve rabies elimination in Sri Lanka.
Rabies geographical distribution encompasses all continents, with the exception of Antarctica. From a global perspective however over 95% of human rabies deaths occur in Asia and Africa, where the domestic dog alone remains the most significant reservoir species and the cause of the vast majority of human deaths. In these regions, dog rabies is responsible annually for millions of suspect human exposures, delivery of more than 14 million post-exposure prophylaxis (PEP) regimens and an estimated 55,000 human rabies deaths. Dog-mediated human rabies is a neglected disease of poverty, affecting underprivileged communities and especially children less than 15 years of age (30% to 50% of all exposures).

Substantial technical progress realized throughout the 20th century led to the development of safe, affordable and efficacious animal and human vaccines, resulting in declining disease burden through control in domestic and wild animals in several developed and developing countries. Today however dog rabies continues to escalate unabated across much of Asia and Africa, due to the low priority still given to control. This is mainly due to a lack of awareness of the true scale and magnitude of the disease burden, as well as misperceptions as to the feasibility, cost-effectiveness and public health benefits of dog rabies control. Thus, a 'paradigm shift' in strategic planning and implementation activities is still needed by the many countries still focusing on PEP as the only means to prevent human deaths. It is a feasible goal, theoretically, technically and logistically, to eliminate human rabies in Asia and Africa through control of domestic dog rabies.

Within the broader context, the goal of this Gates Foundation - WHO project is to prevent human rabies through the control and eventual elimination of canine rabies, creating a paradigm shift for human rabies prevention in Africa and Asia. The project aims to catalyse similar initiatives for the control and elimination of rabies in Africa and Asia within the next decade. The major objectives are to improve delivery of post-exposure prophylaxis (PEP) to exposed patients, to control and eliminate rabies in domestic dogs while improving surveillance/diagnostics and building a strategy ensuring sustainability of the rabies-free status at the end of the project duration. From a short-list of ten countries, sites in three countries - Tanzania, South Africa and the Philippines - have been identified to demonstrate the feasibility, cost-effectiveness and benefits for human health of controlling and eliminating canine rabies in a time period of five years. The 3 selected areas are different so to generate additional information on rate of success according to geographical, demographic, cultural, organizational, tactical and other heterogeneities between the 3 project areas.
SESSION 3. FUNDAMENTAL AND EPIDEMIOLOGICAL RESEARCH

Chair person: Dr. Franka Richard, Rabies Program National Center for Zoonotic, Vector-borne, and Enteric Diseases, Centers for Disease Control and Prevention, US
Co-Chair person: Dr. Herve Bourhy, Pasteur Institute, Paris
Report by: Dr. Franka Richard

This session included a large spectrum of presentations covering topics going from epidemiological studies to pathogenesis, therapy and molecular diagnosis and identification. We heard from Dr Vong that the classical surveillance of rabies in Cambodia lead to an underestimation of the incidence in humans. This presentation highlighted that simple epidemiological models based on local data can help to evaluate the real incidence of rabies in Asian countries.

The surveillance can also be improved by a low cost, real time surveillance for dog bite and rabies as implemented in Pakistan. This surveillance system presented by Dr Khan may also serve to provide onsite decision support for health workers.

This epidemiological part was completed by the presentation of Dr Bourhy showing that many encephalitis including rabies cases remained unexplained mainly because of the absence of clear and validated decision algorithms for diagnosis, because of inappropriate samples collected and because of the lack of large spectrum diagnostic tools. In all these cases resequencing microarrays provide a good alternative to present techniques. Preliminary results indicate that it shows a good sensitivity when used on biological specimens taken from rabid confirmed patients and is able to identify presently unassigned viruses.

The talk of Dr Morrissy illustrated that lyssaviruses different from the classical dog virus may complicate the epidemiology in Asia. He presented the history and the current situation of rabies in bats in Australia showing that different fruit and insectivorous bats are infected by 2 types of Australian bat lyssaviruses. Although the prevalence seems low, these bats exhibit a large geographical distribution covering a large part of Asia. Therefore, this may represent another risk for Asian countries.

This session included 3 talks dealing with the understanding of the pathogenesis of rabies. Dr Hemachuda presented us a large review of the host immune response in the 2 types of clinical presentation: furious and paralytic rabies. He showed that the blood brain barrier remains intact until the coma stage indicating that it is unlikely to play a role in the initial stage of the disease. Several routes of entry may be used by the virus as shown during the presentation of Dr Shantha. This may influence the immunological response and the integrity of the blood brain barrier and allow the entry of immune effectors. Dr Jackson insisted on the role of dorsal route ganglia in the induction of the earliest neurologic symptoms.
Finally, this session brought to our information some new results and hopes concerning new therapeutic approaches for rabies. New products are currently under research and evaluation to provide an alternative to the use equine rabies immunoglobulins.

Dr Franka presented the work of his group on the development of 3 different cocktails of monoclonal antibodies. He reviewed the criteria for selection and the advantages of these products: production on a large scale, production at a higher concentration if proved to be useful, high consistency from batch to batch, elimination of risk associated with equine derived products.

The development of one of these cocktails (two monoclonal antibodies directed against antigenic sites I and III of the viral glycoprotein) was further presented by Dr Bakker. Phase II trials have been achieved or are on going. Phase III trials are planned.

Dr Hemachudha also reviewed new strategies using artificial micro RNA which proved to inhibit virus replication when used in cell culture systems. Both Dr Hemachudha and Dr Jackson questioned the efficacy of the Milwaukee protocol in light of multiple therapeutic failures. Dr Jackson expressed particular concerns about the use of therapeutic coma for rabies.
Acute encephalopathy refers to a state of rapid deterioration of brain function, usually presenting as an alteration in a state of consciousness, with or without focal neurological signs. Worldwide data report an annual incidence of acute encephalitis ranging between 3.5 and 7.4/100,000, or 16/100,000 in children. These neurological syndromes are associated with significant morbidity, mortality as it is the case with rabies or severe, permanent damage including cognitive and behavioural impairment, affective disorders and epileptic seizures. Of the pathogens reported to cause encephalitis, the majority are viruses. However, despite extensive testing, the vast majority of encephalitis cases remain unexplained. So far there is a paucity of systematic studies for the etiological confirmation of cases of acute encephalitis. Various factors are responsible for this underestimation, of which two major causes can be highlighted: 1) the limitation of available information concerning the epidemiology of these infections, leading to an absence of validated decision algorithms for diagnosis, 2) the inefficiency of current routinely diagnostic methods when testing large numbers of known pathogens, when sequence divergence is too high, and especially if new viruses (unsuspected or presently unknown) are involved. In the recent past, diagnosis of viral infections of the CNS and of rabies in particular has been revolutionized by the advent of several methodologies like resequencing high density microarrays and high throughput sequencing, which have opened new possibilities in terms of simultaneous detection and characterization of known and unknown viruses.
Monoclonal antibodies for PEP: status and direction

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A critical part of modern post-exposure prophylaxis (PEP) is neutralization of rabies virus by passively administrated antibodies and clearance of virus through induced active immunity. The availability of costly human rabies immune globulins (HRIG) is very limited and equine immune globulins (ERIG) may cause adverse reactions. Moreover, digested immune globulin fragments from ERIG, widely used for PEP in Asia, effectively neutralize RABV in cell culture, but based upon their use in relevant animal models and field observations in severe exposure settings demonstrated limitations in efficacy are suggestive for improved strategies in PEP. Monoclonal antibodies (mAbs) have been suggested as one possible replacement for HRIG and ERIG since the 1980s. Major advances in biotechnology have made it possible to develop and experimentally evaluate several new murine, humanized or human monoclonal antibody biologics. Multiple experiments conducted in animal models demonstrated that cocktails of at least two (broader neutralization spectrum) mAbs of murine or human origin provide safe and efficacious alternatives to currently used polyclonal serum products. The production of chimeric or recombinant mAbs may eliminate the problems associated with possible adverse effects of heterologous antibodies and shorter half-life. No commercially available mAb products for PEP are in the current market. However, cocktail of two human mAbs, produced in Europe, is entering phase III clinical trials. Similarly, humanized mAbs are being considered for PEP in India and plans for development and production of mAbs for PEP are being implemented in South Korea. To support development of alternative products for PEP multiple organizations offer technology transfer of efficacious cocktails of murine mAbs, already evaluated in animal models, to potential producers and collaborators for further investigation and development, such as production in plants. Based on the available evidence, cocktails of mAbs should provide safe, efficacious, available and affordable replacements for currently used serum products worldwide in the near future.
The currently recommended prophylaxis for individuals exposed to rabies virus is the combined administration of rabies vaccine and rabies immune globulin (RIG). However, limited supply hampers the availability of RIG, particularly in enzootic areas. To circumvent the global RIG limitation we aimed to develop a human monoclonal antibody cocktail, CL184, for rabies post-exposure prophylaxis (PEP) that would replace the plasma origin RIG. CL184 consists of an equipotent mixture of two human IgG1 mAbs, CR57 and CR4098, which are directed against non-overlapping rabies virus glycoprotein epitopes. Previously, we have shown that the in vitro breadth of neutralization of CL184 against a large panel of rabies street viruses of various animal origins as well as in vivo protection by CL184 in a Syrian hamster rabies challenge model was comparable to results obtained with human RIG. A detailed preclinical selection procedure was applied to establish the CL184 antibody combination. In addition, encouraging data from the Phase I (US and India) and Phase II (US) clinical evaluation of CL184 have been obtained. The future availability of CL184 may help to ensure consistent supply of pivotal life-saving biologics to rabies endemic areas and could substantially contribute to the reduction of human rabies deaths, when combined with educational measures and efforts to eliminate canine rabies.
Bat Lyssavirus Epidemiology in Australasia: Evaluating its current and potential public health implications

1 Chris Morrissy, 1Ross Lunt, 1John Bingham, 2Lance Sanders and 1Peter Daniels

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Australian Bat Lyssavirus (ABLV) is endemic in Australia and is found in both megachiropteran (flying fox or fruit bat) and microchiropteran (insectivorous) bats. ABLV was shown to be distinct from classical rabies (genotype 1), and assigned to the new genotype 7. There have been two human cases of ABLV in Australia, in 1996 and 1998, but there have been no known cases in domestic or wild terrestrial animals. ABLV was first identified in Australia in tissues taken from a black flying fox (Pteropus alecto) in 1996. A second case, from 1995, was identified after a retrospective histological examination of archived tissue from the same species. A virus with close serologic and genetic relationships to members of the Lyssavirus genus of the family Rhabdoviridae was isolated in mice from the tissue homogenates of a sick juvenile animal. Since 1996 ABLV has been isolated from bats in every year except in 2008.

The four largest species of frugivorous bats in Australia are called flying foxes and belong to the genus Pteropus (Order Chiroptera, Suborder Megachiroptera, Family Pteropodidae). The Australian range of the flying foxes extends from temperate eastern and coastal Australia into the eastern tropics, around the tropical northern coastline, and down as far as the subtropical west coast. The gray-headed flying fox (Pteropus poliocephalus) range is the temperate and subtropical east coast, the black flying fox (P. alecto) inhabits primarily the subtropical and tropical range, and the little red flying fox (P. scapulatus) occupies the entire range except the coolest southern areas. The fourth species, the spectacled flying fox (P. conspicillatus) occupies a smaller range in tropical northeast Queensland. Flying foxes roost together in large numbers, in "camps", containing possibly tens of thousands of animals, often with more than one species present.

Australia uses rabies vaccine for pre-exposure prophylaxis for bat lyssavirus in a manner as is recommended for rabies. Pre-exposure prophylaxis with rabies vaccine is recommended for: People in Australia liable to receive bites or scratches from bats (this includes bat handlers, veterinarians, wildlife officers and others who come into direct contact with bats), expatriates and travellers who will be spending prolonged periods (ie. more than a month) in rabies-endemic areas. (NB. This time interval, of more than a
month, is arbitrary, and rabies has occurred in travellers following shorter periods of travel), People working with mammals in rabies-endemic areas, and Research laboratory personnel working with live lyssaviruses.

Both human rabies immunoglobulin (HRIG) and rabies vaccine are available for post-exposure treatment.

AAHL is the Australian national reference laboratory for rabies and Australian bat lyssavirus. The diagnostic capability includes the fluorescence antibody test (FAT), polymerase chain reaction (PCR) and sequencing, virus isolation in Neuro 2a and MNA cells and suckling mice and immunohistochemistry for agent detection and identification and the rapid fluorescent focus inhibition (RFFIT) test and fluorescent antibody virus neutralisation (FAVN) test (virus neutralisation assays) and ELISA for serology to confirm vaccine response in humans and in animals for certification in pet travel schemes. AAHL has recently conducted trials of a rapid test for rabies, the BioNote One Step rabies antigen test kit, for detection of ABLV and will provide some data on test performance.

ABLV remains a risk to human and animal health in Australia and is controlled by avoidance of bat/human contact through public awareness, destruction and testing of suspect bat cases, vaccination of in-contact humans and destruction and monitoring of in-contact pets along with the controls put in place for the prevention of rabies entering Australia.
Pathogenesis of disease caused by lyssavirus, particularly rabies of genotype 1, remains enigmatic. Although studies in experimental rodent model using genetically engineered virus yield useful information, some may not be relevant or applicable to the understanding of human disease.

Eclipse period has been hypothesized to be the effect of tissue (muscle) specific microRNA. After successful entry into the nerve, virus gains access to the brain and spinal cord sometime before symptoms develop. Presence of the local prodromal symptoms and signs does not necessarily reflect that virus just reaches the nervous system or the dorsal root ganglion (DRG). Such local symptoms are the results of inflammatory responses to infected DRG neurons. These responses may be developed even after the virus has moved out in centrifugal pattern from the CNS to peripheral organs, and start initiating host immunity to rabies virus. Magnetic resonance imaging (MRI) could demonstrate changes in the brain, brachial plexus and spinal cord and root at least 2 days before electrophysiological (EP) evidence DRG pathology appeared. At this stage, the patient had only pain at the bitten arm but was fully conscious and did not manifest any signs of rabies nor having any EEG changes. This confirms the early subclinical invasion of virus into the CNS. In furious rabies, despite no demonstrable limb weakness, EP signs of anterior horn cell dysfunction were noted in the corresponding segment of the bite site such as in the hand/arm region as early as 3 days after the clinical onset. This subsequently involved contra-lateral limb and then further rostrally to neck and caudally to the thoracic and lumbar segments. In paralytic rabies, peripheral nerve dysfunction is responsible for weakness. EP studies do not confirm anterior horn cell dysfunction as in the case of furious rabies. Demyelination or axonopathy of peripheral nerve, likely to be due to immune mediated changes, is the underlying mechanism of weakness in paralytic rabies.

Immune responses in rabies patients may vary according to the type of virus variants (dog vs bat), timing of testing, or the techniques used. Serologic data from patients with rabies in the Western hemisphere and in Europe differed from those from patients in dog rabies endemic countries. Antibody is usually developed in the sera and CSF if the patients survive more than 8 days in the former whereas it is unpredictable in the latter. Further, it remains unexplained why neutralizing antibodies in serum and CSF and immune complexes in the CSF can be found in approximately 50% and 75%
respectively in paralytic patients in India. None of 43 patients from Cambodia and Africa had CSF rabies antibody during the whole clinical course. Our earlier study showed a stronger cell mediated immune response in the blood of furious rabies than paralytic patients. This may not reflect immunopathogenetic mechanism. A larger quantity of rabies virus in the brain and spinal cord of furious (than paralytic patient) that later centrifugally spreads to peripheral organs should elicit such a strong systemic immune response especially in furious rabies patient. Our recent study in naturally infected dogs, ideal model in studying of human rabies pathogenesis, confirms this hypothesis. Brains of paralytic dogs contain less amount of viral RNA than those of furious dogs. On the other hand, paralytic dogs have stronger CNS immune response (as determined by the presence of cytokine mRNA transcripts) and more MRI disturbances than furious dogs. The degree of MRI changes is correlated with CNS immune response rather than the amount of virus.

Blood brain barrier (BBB) of rabies infected patients and dogs is intact until they are in coma despite the presence of cytokines in the brains, known to affect the integrity of BBB. Immune responses in the brains disappear during late stage. Proteomic techniques [2 D gel electrophoresis followed by mass spectrometry (MS) and MS/MS] were employed in hippocampus, brainstem and spinal cord tissues of normal, furious and paralytic late stage (6 of each) dogs. Early apoptotic stage proteins were found in hippocampus. Heat shock-innate immunity, antioxidant and cytoskeletal proteins were found increased in brainstem and spinal cord especially in paralytic rabies. Collapsin response mediator protein- 2 was increased in brainstem and hippocampus but decreased in spinal cord of paralytic rabies. There was no evidence of aggressive adaptive immunity. Cell infiltrations were scarce in the brain tissues. These suggest that postponing or delaying death to buy the time until systemic immune response (cells and/or antibody) takes place and subsequently ingresses into the brain compartment may not be valid.

Artificial microRNA (amiRNA) was also probed to determine its potential therapeutic benefit. Single and multiple targeting amiRNAs against challenged virus standard (CVS) rabies mRNA was constructed and tested in CVS as well as viruses with imperfect matches. Single or multiple targeting amiRNA against CVS-rabies N mRNA yielded an efficacy of 95% reduction of CVS, street and HEP-Flury viral genome. amiRNA may be beneficial once appropriate delivery system is developed.
Objective:
The object of this presentation is to show the perineural epithelium (PE) of the olfactory mucosa, nerves, bulb; and taste buds nerves and other sensory and motor end organs; and their role in transfer of rabies virus to the CNS (1). We want to discuss possible new approach in the treatment of rabies patients based on our findings using insulin and various antirabies therapies to treat rabies patients.

Material and Methods:
Studies were made on the Rhesus-squirrel monkey, rat and rabbit' olfactory mucosa, olfactory nerve and bulb, taste buds and various sensory and motor end organs. They were sectioned and stained with various histochemical methods. They were dissected under high power dissection microscope to delineate various coverings of the nerve supply and the origin of their coverings in relation to pia-arachnoid membrane and subarachnoid space of the CNS. The effect of virus transfer and the role various components of peripheral nerves (PNS) were studies at CDC of Atlanta, though not on olfactory mucosa itself.

Results:
Our studies show that the olfactory nerves and the taste buds nerve supply are covered completely by Peter cell covering, which are directly continuous with the pia-arachnoid mater of the CNS and SAS with CSF. The subarachnoid space with CSF surrounding the olfactory bulb is continuous with the space surrounding the olfactory nerves as they emerge from the olfactory bipolar cells of olfactory mucosa. This is in turn is continuous with the SAS of CNS and Spinal cord and the eye. Except for the fine nerve terminals such as pain fibers and autonomic nerve endings, the entire peripheral nervous system including various sensory and motor end organs are covered by perineural epithelium which isolates them from the surrounding tissues and also allows the transfer of agents to and from the CNS. Studies conducted at CDC rabies center showed that this membrane does facilitate the conduct ion of rabies virus (1, Baer et al). When this membrane was removed, there was a 20% delay in conduction of the virus to the brain. Amputation or cutting a segment of the nerve early prevented the development of the disease after rabies virus injection. Our studies on insulin in bacterial, viral, diseases, autoimmune diseases, and cancers show that we can enhance the therapeutic agent uptake, enhance their activity and promote their dissipations to treat these life threatening conditions. We want to use the same method in rabies for pre and post exposure.
prophylaxis (PEP) and treatment of rabies patients (6). The olfactory cells are dying 10,000 every year or about 30 cells every day. The death results in space between supporting cells which is continuous from the mucus coating all the way to the nerve fasciculi which enter the CNS and its surroundings. This results in a porous (not so barrier) like olfactory mucosa. Hence the rabies virus (other microbes) and therapeutic agents can easily enter the various components of the CNS through olfactory route (Shantha and Nakajima, Z. Zellforsch. 103. 291-319; 1970). The blood supply of the nasal mucosa can also carry the virus to the various nerve supply (CRN-V) of the nose through the Virchow-Robin space of peripheral nerves and then to CNS (1).

**Method of Rabies treatment:**

Based on our experience on insulin and its effectiveness, we want use it along with various therapeutic agents and modalities in the treatment of Rabies and PEP. The principle methods I propose to treat Full Blown Rabies Cases are (6) Intranasal administration of antirabies therapies including monoclonal antirabies and anti TNF MAB, epoetin, IGF-1, nerve growth factors etc, to reduce the brain inflammation and neutralize the rabies virus; using insulin as enhancer of uptake form olfactory mucosa and carry them to the brain. Antirabies therapies through subarachnoid space with insulin using a SAS indwelling catheter to deliver to CSF. Intravenous or intra-arterial antirabies therapy after BREAKING THE BLOOD BRAIN BARRIER to get it into the substance of the brain with insulin pretreatment to enhance the NEUROPILE uptake and transfer across BBB..Intraventricular delivery of antirabies therapies with insulin with Ommaya device.

Enhance the immune system by orally administering the immune stimulating component of the rabies virus and / or other such immune enhancer through NG tube or Gstro-jeunostomy tube to stimulate the plasma cells(180,000 /cubic mm) in the lamina propria of the intestines at the same maintain proper nutrition. We can also use y IM or IV or SQ injection routes of highly effective rabies antigens with insulin to produce neutralizing rabies antibodies rapidly.

Lower the metabolism of the brain by lowering the blood sugar level, what I call INTERMEDIATE HYPOGLYCEMIA every two to 6-8-12-24 hours once to enhance the uptake of neutralizing antirabies antibodies and therapeutic agents and enhance the production of antirabies antibodies.

Supportive critical care therapy with Critical care monitoring as enumerated in Milwaukee protocol (MP). All these modalities are discussed during the presentation.

**Discussion:**

Based on these histological findings, it is clear that any bacteria and virus such as rabies virus can get easily attached to the sticky mucus coatings, olfactory cilia and microvilli of these sensory end organs (figs. 1, 2, 3). They can reach the central nervous system neuropile and subarachnoid space CSF without any hindrance through these anatomical routes within the axons (3) and its surroundings; and below the sub Perineural epithelial space to reach the CNS resulting in rabies infection to the CNS. Blood vessels can also act as conduits in transfer of the rabies virus. Based on our experience of breaking the blood brain barrier (BBB), we believe that the MAB anti rabies antibodies (5), other antiviral agents (4) and therapeutic agents as well as neuroprotective agents can be delivered to the brain through the nasal olfactory mucosa and intra arterial and / or
intravenous methods after breaking the BBB and the other above discussed methods for the treatment of rabies. With intensive care, directly attacking the rabies virus in the brain as describe above; and stimulating the natural antibody production; the rabies virus can be cleared and the damage to the brain is minimized with possibility of full recovery of the patients with least neurological deficit.

Conclusions:

The most elusive route debated is inhalation and oral route of rabies virus transfer (2, 3). We have shown how easy it is for rabies virus (and other microbes and therapeutic agent) to reach the CNS from inhalation and oral routes. By using the olfactory mucosa as histological route; anti rabies antibodies (MAB) and various antiviral agents; combined with insulin as uptake, activity and dissipation enhancer; can be directly delivered to the CNS to neutralize the rabies virus in the treatment of rabies along with other intensive care with life support interventions. We describe 7 prong attacks on fully developed rabies patients to clear the virus and possibly save the patient life

Figure 1. Showing the olfactory mucosa as the portal of entry of rabies virus from the virus containing air inhalation. Note the perineural epithelial covering of the olfactory nerve fasciculi and the space created by the dead olfactory sensory neurons acts as a passage for entry of rabies virus and delivery of therapeutic agents to CNS. .
Figure 2. Showing the histological route of rabies virus and various antirabies therapeutic agents transfer to the brain from olfactory mucosa to the CNS and CSF.

Figure 3. Showing the taste bud pore as the portal of entry of rabies virus when exposed orally with direct contact with the tongue. Note the perineural epithelial covering of the taste bud nerves.
Recent developments in understanding human rabies using animal models

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Natural rabies in humans and animals is characterized by inflammatory changes and a paucity of degenerative neuronal changes. This has led to the idea that neuronal dysfunction may explain the severe clinical disease and fatal outcome in rabies. Recent studies in experimentally infected mice has shown that there are advanced structural changes affecting neuronal processes, including dendrites and axons, which may explain the severe disease in the presence of only mild histopathological changes.

Dorsal root (sensory) ganglia are often infected in human rabies and this involvement explains the earliest neurologic symptoms. There are inflammatory changes in dorsal root ganglia that are associated with degenerative changes in gangliocytes, which are out of proportion with what is observed in central nervous system neurons. Neuronal death likely occurs by autophagy. Neuronal apoptosis is not likely of pathogenetic importance in human rabies.

Recent studies using intravenous administration of large doses of bat rabies virus in mice show viral entry at the neurovascular interface of the hypothalamus-hypophysis system. However, these studies probably do not provide useful information on how rabies virus spreads to the central nervous system under natural conditions or how transmission of rabies virus infection occurs after organ transplantation.

Can our knowledge of rabies pathogenesis from experimental models be applied to help us successfully treat human rabies? Recent studies indicate the importance of entry of immune effectors through the blood-brain barrier, and approaches manipulating blood-barrier permeability may be fruitful. Experimental studies in a mouse model cast doubt on the efficacy of therapy with ketamine. The use of therapeutic (induced) coma lacks scientific rationale and should be abandoned. New therapies such as selective cerebral hypothermia using a cooling helmet or intranasal cooling should be evaluated. Novel approaches need to be taken for therapy of this ancient disease.
Assessing the Burden of Rabies through an Epidemiological Survey: Challenges and Opportunities. Establishing low-cost, real time surveillance for dog bite and rabies in Pakistan

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Background:
Dog bite and rabies data for Pakistan are very limited, and reliable national estimates are unavailable. Routine surveillance for dog bites and rabies at rural and urban referral centers needs strengthening to improve dog bite management and provide estimates.

Methods:
We are using GPS-enabled cell phones to capture real time data on dog bites presenting to major referral centers in selected rural and urban districts. All patients presenting to the selected emergency rooms with an animal bite or reporting contact with a possibly rabid dog and all patients admitted to hospital isolation rooms with suspected rabies are screened for enrollment in the study.

Interim results:
82% of dog bite cases reported are male, primarily in the age group of 5-14 years. Rabies immunoglobulin is not applied on all Category III wounds in 3 of the 5 centers where surveillance has been established to date. At 3 of the 5 centers, rabies vaccines are either not available or the sheep brain vaccine produced by the government National Institute of Health is used instead of tissue culture vaccines. Two cases of rabies have been identified in hospital isolation rooms thus far.

Discussion:
Symptomatic rabies patients particularly in the rural areas are not likely to be brought to the hospital due to distance, lack of information. Routine, real time surveillance for dog bites can be established at relatively low cost using cell phones at major referral centers in a developing country. Cell phone based data capture can serve as a strong advocacy tool by helping visualize the daily/weekly count of dog bites and may also serve to provide onsite decision support systems for health workers to improve dog bite management according to WHO guidelines.
Assessing the burden of rabies in Cambodia: Challenges and Opportunities

Dr. Sirenda Vong M.D., MSc. et al.,
Paris Pasteur Institute in Cambodia

Rabies, a fatal but preventable zoonosis, is a major public health problem in developing countries. In Cambodia the disease burden is largely underestimated because patients with encephalitis following dog bites are rarely hospitalized and die at home. Since 1998 Institut Pasteur in Cambodia (IPC), Phnom Penh has been the only source of free post-exposure prophylaxis (PEP) and post-mortem diagnosis. As a national rabies control program is not operational yet, IPC has been the solely reliable source of information on human cases collected in Cambodia. We report the results of an analysis of the 1998 - 2007 IPC data on (i) all post exposure treated patients, (ii) confirmed human rabies cases and (iii) human and animal specimens testing to describe the epidemiological situation of rabies in Cambodia. We also estimated the dog population piggybacking on three surveys for avian influenza conducted in rural areas in 2005-2007. Finally, we used the 2007 IPC data to estimate the incidence of rabies related human deaths in Cambodia from passively reported dog injury statistics.

During 1998-2007, 124,749 patients received PEP at IPC (average 12,470; range 8,907 - 14,475) and 63 fatal human cases presenting with encephalitis following a dog bite were reported, in which 73% were confirmed positive by direct immunofluorescence assay or by reverse-transcriptase polymerase chain reaction. During 1998 - 2007, IPC tested 1,255 animal brain samples, 1,214 (97%) were from dogs including 610 (49%) positive samples.

In 2007, 14,475 patients received PEP (100 PEP/100,000 people in Cambodia) including 95% who resided in Phnom Penh (615 PEP/100,000) or 5 neighboring provinces. The predictive model estimated 810 human rabies deaths would occur in 2007 (95%confidence interval [CI] 394 - 1,607); an incidence of 5.8/100,000 (95%CI = 2.8 - 11.5). Of the 1,538 households of 151 villages in seven rural provinces that were surveyed during 2005 - 2007, 75% of the households owned at least one dog. A total of 2,670 owned dogs were recorded for 8,269 individuals surveyed yielding a ratio of 1 dog to 3.1 humans (95%CI 1:3.0 - 1:3.2). Only 17 (1.4%) dogs were reported to have been vaccinated against rabies. We calculated that the dog population could be up to 5 million dogs considering an 84% dog ownership.

Conclusions: Access to PEP is only sufficient for Phnom Penh residents: only one free PEP clinic in Phnom Penh with no control interventions in dogs is not sufficient to handle a country in which rabies transmission occurs endemically. In 2007, the estimated
rabies related mortality exceeded that of malaria and that of dengue. The present analysis represents an important contribution in bringing rabies to the attention of Cambodia national authorities where rabies is often perceived as a rare disease because of the lack of incidence data. Actual population-based surveys are still needed to validate the model. Nevertheless, we recommend establishing a comprehensive national rabies control program whose one of the major challenges would be to work across ministries and agencies to ensure continued political commitment and active community participation so that proper WHO recommended rabies vaccines are available and accessible to Cambodians and rabies transmission in the dog population is controlled. RIACON partners should actively assist countries in lobbying to national policy makers, raising funds for assessments and national control programs and developing public and private partnership to reduce costs of vaccines.
SESSION 4. SCIENTIFIC AND ADVANCED RESEARCH

Chairperson: Dr. Alan C Jackson, University of Manitoba, Canada.
Co-chair person: Dr.B J Mahendra, Executive Director, RIA Foundation.
Reported by: Dr.B J Mahendra, Executive Director, RIA Foundation

This session included various presentations on different issues on advanced research.

Dr Anita presented the neuropathological changes in rabies. She concluded that even though rabies and GB syndrome are clinically similar, they differ in immunopathology & following rabies vaccination, the pathology mimics GB syndrome with upregulation of T- cell response reflecting common immunopathogenetic mechanism.

Dr Thomas Mathew described regarding how IDRV was implemented in Kerala and attributed its success to a broad based ownership including political commitment, Scientific advocacy, technical & administrative efficacy & involvement of medical colleges and health services.

Dr D M Satapathy highlighted the challenges faced in IDRV, which included high dropout rates, intradermal administration in children below 6 years & How to go about if RIGs is not available/affordable.

Dr Ashwath Narayana briefed about the clinical trials with PDEV in India manufactured by Zydus Alidac. He told about the various studied conducted in India starting from its inception to the comparative trial with various international WHO approved vaccines.

Recommendations:
- Continued research on pathological & immunological changes in rabies.
- Need to explore various models to implement IDRV successfully.
- Explore the challenges in IDRV and to find out the solutions with standard guidelines.
- PDEV manufactured in India is Safe, tolerable & immunogenic as other WHO approved vaccines when administered intramuscularly.
Background:

Rabies is an important public health problem in developing countries like India where an alarmingly high incidence is reported every year despite availability of highly effective, and safe vaccines. In clinical practice, diagnosis of furious (encephalitic) form of rabies poses little difficulty. In contrast paralytic form poses a diagnostic dilemma, as it closely mimics Guillain Barre (GB) syndrome. The problem is further compounded in absence of history of dog bite.

Objective:

To determine differences in clinical, pathological and pathogenetic aspects between GB syndrome and paralytic rabies.

Material & Methods:

Clinical features, and neuropathological findings among 40 autopsy confirmed cases of paralytic rabies were studied. The neuropathology and immunophenotypic features in spinal cord in seven cases of paralytic rabies (vaccinated-2) were compared with GB syndrome (n=9). Cytokine levels (TNF, IL4, IFN and IL6) in CSF were estimated by standard ELISA technique.

Results:

Clinically, presence of fever at onset, paraesthesia, fasciculation and flaccid weakness confined to bitten extremity, rapid deterioration with encephalon and autonomic involvement, peripheral blood leucocytosis and CSF pleocytosis with electrophysiology demonstrating peripheral nerve demyelination or axonal degeneration unlike conduction blocks in GB syndrome were important pointers to the diagnosis of rabies. On neuropathological examination of spinal cord, variable inflammation, microglial response forming nodules and neuronophagia signifying ongoing encephalomyelitis was common to both while radicals of spinal roots showed variable inflammation and focal demyelination involving the posterior and lateral columns corresponding to clinical symptomatology. In cases of paralytic rabies, Negri bodies were discernible within dorsal root ganglion in one case while immunohistochemistry revealed abundant rabies viral
nucleocapsid antigen within the neurons of anterior and posterior horns in diffuse or speckled patterns and focal spread of viral antigen was also evident in spinal nerve roots. Interestingly, immunophenotypic differences in inflammatory infiltrates were seen. In GB syndrome, CD68 positive macrophages and CD8 positive T cells predominated in keeping with its autoimmune T cell mediated pathogenesis. In contrast, in cases of paralytic rabies, infiltrates were predominantly macrophages without T cells. This corroborated with high levels of anti inflammatory cytokines (IFNγ and IL6) and low levels of TNFα and IL4 that abrogated the Th2 response. Intriguingly, in cases of paralytic rabies that were vaccinated, histomorphologic and immunophenotypic features were similar to GB syndrome suggesting a similar immunopathogenetic mechanism.

**Conclusion:**

Paralytic form of rabies and GB syndrome though clinically similar differ in immunopathology. Following rabies vaccination, pathology mimics GB syndrome with upregulation of T cell response reflecting common immunopathogenetic mechanism.
Kerala, a state with health indicators at par with the developed countries, has to its credit the highest literacy rate of 93% for women and 96% for men attained by any state in India (NFHS-3). Kerala has also achieved remarkable improvements in the various demographic parameters. The mortality in Kerala is only half as in the rest of the country as a result of widespread accessibility to medical care, high utilization of the facilities and the wide coverage of inoculations among the population. It was the first state in India to phase out the use of nervous tissue vaccines and introduce CCV.

Kerala has started implementing IDRV since February 2009. IDRV has been made available in all the major hospitals in Kerala, including the 5 medical colleges and is currently being extended to the entire district and taluk hospitals of the state. This has materialized due to the synergistic support from the Department of Health, Govt of Kerala by providing the Administrative support and Academic inputs from dedicated members of APCRI, which showed the commitment of the association towards the achievements of its organizational goals. The following activities were undertaken at the state level:

September 20 & 21, 2008: A workshop "IDRV KERALA" which was attended by over 300 delegates from all over India led to the development of operational guidelines and guidelines for implementation.

July 4 & 5, 2009: National conference of APCRI "APCRICON 2009" was successfully conducted which was attended by about 200 delegates from across India. In addition many hands on training were arranged for the medical officers, health inspectors and nurses. Also, numerous CME’s for doctors and other stake holders were organized across the state.

The success of this programme in Kerala can be attributed to the broad base ownership build for IDRV in government medical colleges and also in the district health services. The Kerala experience shows that in order to translate policy to practice requires the back up of technical, administrative, political and scientific advocacy. Some of the weakness that were identified were the non involvement of the private sector, lack of IDRV facility at the PHC level and also the inability to provide IDRV round the clock at all the centres.

Despite the shortcomings IDRV provides a foundation to develop enormous opportunities to provide vaccine free of cost to all patients and also achieve greater acceptance among the public. Efforts are currently underway to address the weaknesses and ensure implementation of IDRV in as many centres as possible to achieve our goal of Rabies free Kerala by 2015.
Challenges in Intradermal Rabies Vaccines (IDRV)

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Objectives:

To highlight the challenges in Intra Dermal Rabies Vaccination. The tripod of Anti-Rabies treatment stands on local wound care, administration of RIG and active immunization against Rabies. The use of cell culture vaccine has made the process of active immunization into a painless, effective and safe option than the previously used reactogenic & low potent NTV. The Essen regimen has been a time-tested method of active immunization but the use of this regime in public health practice lays a huge burden in the Govt exchequer. In a country like India, where more than 10 million post-exposure doses of CCV have to be administered, the Essen regime is not only costly but also not feasible.

Intradermal Rabies vaccination using modern cell culture vaccines has been approved by WHO and the modified TRC regime uses approved by the DCGI in India vide letter No. X-11026/23/05-D, Dated 2/5/2006. The modality of IDRV has been started in the state of Orissa since 27.4.07. As of July, 2009 the Anti-Rabies Clinic of MKCG Medical College, Berhampur, Orissa, India has administered to more than 11,000 cases requiring Post-Exposure treatment.

However the following challenges have been faced in IDRV:

1. Difficulty in administration of intradermal injections over two sites to children especially in the age group of 1-6 years.
2. The regime to adopt in cases who report late to the ARC.
3. The regime to adopt to cases who are unable to afford RIG.
4. The method to tackle the high drop-out rate from Day 7 to Day 28.

These situations need to be addressed, so that effective anti rabies treatment can be carried out in the vast geographical area of a country like India.
Cell culture vaccines (CCV) and purified duck embryo vaccine (PDEV) are currently recommended by WHO for post exposure rabies prophylaxis. In India, purified duck embryo vaccine (PDEV) is manufactured by Zydus Cadila, Ahmedabad, Gujarat from 1998, after a successful transfer of technology from Berna Biotech, Switzerland. The last batch of PDEV (Lyssavac) was produced by Berna Biotech, Switzerland in 2003. Presently, India is the only country where a highly purified PDEV is being manufactured. PDEV is exported to many countries as Lyssavac & marketed in India as Vaxirab.

This presentation will highlight on some of the clinical studies done to demonstrate the safety and immunogenicity* of this vaccine among the Indian population.

After registration of the PDEV in India, a post marketing, phase IV, multi-centric study (IPM, Hyderabad; KIMS, Bangalore & PII, Kolkata) was conducted among 150 animal bite cases. All the animal bite cases were administered PDEV (Vaxirab, Potency: 7.17 IU/ IM dose) intramuscularly as per Essen regimen (1 mL of vaccine on days 0,3,7,14 & 30) & cases with Category III exposures were administered ERIG as per WHO. The results of the study showed PDEV (Vaxirab) was safe & produced adequate rabies virus neutralizing antibody (RvnAb) titres from day 14 to day 365.

To compare the safety & immunogenicity of PDEV (Vaxirab) produced by Zydus Cadila with PDEV (Lyssavac) produced by Berna Biotech, Switzerland, a study was conducted among 220 adult healthy volunteers. All these subjects were administered either Vaxirab (Potency: 8.94 IU/ IM dose or Lyssavac (Potency: 6.4 IU/IM dose) intramuscularly (1 mL) on days 0,3,7,14 & 30. This study was conducted at KIMS, Bangalore & IPM, Hyderabad. The results of the study showed that the indigenously produced PDEV (Vaxirab) was equally safe and immunogenic as the original PDEV (Lyssavac) manufactured at Switzerland.

Subsequently, another study was conducted to assess the safety & immunogenicity of PDEV (Vaxirab, 1mL; Potency: 8.0 IU/IM dose) with two other WHO approved CCVs viz: Purified chick embryo cell vaccine (Rabipur, 1 mL; Potency: 8.51 IU/IM dose) and Purified vero cell rabies vaccine (Verorab, 0.5 mL; Potency: 13 IU/IM dose). This was a multi centric study done at 4 centers (IPM, Hyderabad, KIMS, Bangalore, MKCG Medical College, Berhampur, Orissa & J J Hospital, Mumbai). It was an open label, randomized, phase IV comparative clinical trial involving a total of 152 subjects with animal bite. All the animal bite cases were administered vaccines
intramuscularly as per Essen regimen on days 0,3,7,14 & 28 & cases with Category III exposures were administered ERIG as per WHO. All the subjects had neutralizing antibody titers by day 14 (>0.5 IU/mL) and geometric mean titers (GMT) observed for the 3 vaccines on all days tested (days 14, 28, 90 and 180) did not vary significantly. Side effects were minimal and did not vary significantly among the different vaccine groups. Hence, it was concluded that PDEV (Vaxirab) manufactured by Zydus Cadila, India is as safe, tolerable and immunogenic as both PCEC (Rabipur) and PVRV (Verorab), when administered intramuscularly.

The sera of subjects from the above 3 studies, were tested for RvnAb titers by RFFIT at National Institute of Mental Health and Neurosciences, a WHO collaborating center for research & reference for rabies, Bangalore, India.
Molecular characterization of the complete genome of a rabies virus isolate from India

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Rabies is a zoonotic disease that still remains a major public health problem in South East Asia. Cases in this part of the world contribute to 70% of the global burden. A large number of the cases occur in India. There is however, no organized system of surveillance to assess the disease burden annually. Moreover, comprehensive molecular epidemiological studies have not been performed on Indian isolates. We determined the complete nucleotide and deduced amino acid sequence of a primary isolate of rabies virus obtained from the brain of an infected individual. Comparison of the complete genomic sequence with those of the ten fully sequenced rabies strains available in the GenBank showed nucleotide homology ranging from 97% with AY956319 (Germany, ex-India) to 81% with AY705373 (SHBRV strain). Amino acid homology of nucleoprotein ranged from 99.7% with AY352493 to 92% with DQ875051. In case of glycoprotein gene, the homology ranged from 98.8% with AY956319 to 87.2% with AY705373. An extensive nucleoprotein, glycoprotein and full-length genome-based phylogenetic analysis was performed along with sequences available from the GenBank. Phylogenetic analysis of the complete genome sequence indicated that this isolate exhibited close homology with the ex-Indian strain AY956319. For the first time in India, a complete genome analysis of a rabies virus isolate was achieved. The characterization and phylogenetic analysis of this full length genome emphasizes the underlying genetic diversity amongst the circulating strains in the country.
Comparative evaluation of human embryonic kidney cell line (HEK 293) and Neuro 2a and BHK21 cell lines for rapid isolation of street and fixed rabies viruses

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Isolation of rabies virus is generally done using mice inoculation or infection of susceptible cell lines such as Neuro2a, BHK 21, CER or BSR. Isolation of rabies virus is necessary for confirmation of rabies in cases where rapid diagnostic technique is negative or doubtful. Virus isolation is also required for epidemiological surveillance and genetic characterization of isolates from different parts of the world. In this study we have evaluated a continuous cell line derived from kidney of human embryo. This cell line called HEK 293 was found to express several neuronal proteins including muscarinic acetyl choline receptors. Therefore, we postulated that this cell line could be highly susceptible for rabies virus infection. In this study we evaluated the utility of this cell line for rapid diagnosis of rabies in comparison with other cell lines such as Neuro2a and BHK 21 which are already in use. We tested 75 animal brains belonging to different species and also 10 human brains positive for rabies by FAT. We found that the isolation rate using both HEK 293 and Neuro2a was 100%, while it was only 60% with BHK 21 cells. We conclude that HEK 293 cell line is as sensitive and specific as Neuro2a a cell line for rapid isolation of rabies virus. This cell line which is easy to grow and maintain could serve as an alternative cell line both for rabies diagnosis and research.
Comparative evaluation of a newly developed direct rapid immunohistochemistry test (DRIT) and the fluorescent antibody test (FAT) for rapid diagnosis of rabies in animals and humans

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The Fluorescent Antibody Test (FAT) is considered the gold standard for rabies diagnosis. Due to the cost involved in obtaining and maintaining a fluorescence microscope and FITC-labeled rabies conjugates, most laboratories in India and other developing countries still continue to rely on the detection of Negri bodies for rabies diagnosis. The CDC has developed a new direct rapid immunohistochemical test (DRIT) for diagnosing rabies. The DRIT is a simple and economical procedure intended for enhanced, decentralized surveillance under field conditions, and suited for economical resource constraints in developing countries. This technique is based on identification of rabies virus nucleoprotein (N) in formalin fixed brain impressions with a biotinylated N monoclonal antibody cocktail and subsequent color development - by adding streptavidin peroxidase and amino ethyl carbazole (AEC) - The inclusions can be visualized by ordinary light microscopy within the neural tissue based upon an anatomic-pathologic interpretation. In this study we have evaluated the DRIT for the first time in India which has high burden of animal and human rabies cases. We tested 82 animal brains and 11 human brains by the DRIT in our laboratory in parallel with the standard FAT. There was 100% correlation between the FAT and the DRIT. Based upon these preliminary results, we conclude that this new technique is both sensitive and specific for the diagnosis of rabies and should be considered as a cost effective diagnostic technique for rapid diagnosis of rabies in developing countries.
Enabling Rabies Post-Exposure Prophylaxis in India: Intradermal Vaccination Devices

Authors: PATH ID Rabies Team (Zehrung, D; Lewis, K; Nundy, N; Jarrahian, C; Kaipilyawar, S; Patwardhan, M)
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Introduction:
In India approximately 3 million bite victims seek post-exposure prophylaxis (PEP) every year and millions more do not seek treatment or do not have access to PEP due to the high cost and vaccine supply shortages. Intradermal (ID) delivery of rabies vaccine is dose sparing and the WHO has recommended this method since 1991 (WHO, 2007). The conventional ID injection technique is difficult to use and inconsistent in accurately delivering ID injections. New ID delivery technologies could enable health care personnel to deliver rabies vaccine intradermally, thereby reaching more people exposed to rabies in a timely manner.

Methods:
PATH, a non-profit public health organization headquartered in Seattle, WA and with multiple offices in India, collaborated with a network of academic and industry partners, including the Institute of Preventative Medicine (IPM) and Indian Immunologicals, Ltd (IIL), to identify and qualify dose-sparing ID vaccination devices and demonstrate their clinical feasibility. Two ID injection devices, a needle adapter and a needle-free jet injector, were included in preclinical device mechanics and immunology studies, as well as in a user acceptability field assessment conducted among public-sector Indian health care workers.

Results:
Preclinical studies demonstrated that these devices can successfully deliver liquid to the intradermal layer of the skin and that rabies vaccine produces adequate levels of antibodies, similar to ID delivery by a conventional needle and syringe. The user acceptability field assessment demonstrated that both devices are generally acceptable to Indian health care workers and that the devices have the potential to benefit the Indian health care system by enabling ID dose-sparing regimens.

Conclusion:
PATH plans to conduct additional evaluations of these ID vaccine devices for delivering rabies PEP in India. In collaboration with IPM and IIL, a Phase II safety and immunogenicity clinical trial is anticipated to begin in November 2009. In order to determine the economic and commercial feasibility of these devices, PATH also plans to conduct a value proposition analysis.

References:
Assessing awareness of rabies characteristics and prevention in Cambodia

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Background:

It is estimated that 95% of human rabies deaths occur in Asia and Africa, however there is a lack of case data in Cambodia on incidence of the disease and associated risk factors. In collaboration with the National Veterinary Research Institute (NaVRI), VWB/VSF-Canada conducted a survey to provide baseline information on people's awareness of rabies in urban and peri-urban areas of Cambodia.

Objectives:

The objectives of this study were to determine knowledge of canine and human rabies, knowledge and practice of health-seeking behaviours, dog ownership practices, and attitudes of proposed rabies prevention and dog population control measures, in Phnom Penh and Kandal province.

Methods:

A household questionnaire was developed and piloted. A cluster sampling methodology proportional to size was used and 250 households were selected and surveyed across 25 villages in Phnom Penh and Kandal province. A descriptive analysis of the results is provided.

Results:

Knowledge of rabies: 93%(233/250) of respondents had heard of the disease rabies. Of those that knew of the disease, 94%(220/233) had seen or heard of a case of canine rabies and 44%(102/233) of a human case. 84%(196/233) were able to describe without prompting two or more indicators of rabies in dogs. 77%(180/233) understood that rabies causes death in humans. 52%(121/233) had heard of a rabies vaccine for dogs.

Dog ownership: 56%(141/250) of households interviewed owned at least one dog. Of the dog-owners surveyed, only 13%(19/141) kept their dogs confined and inside their property day or night.

Dog bites: 92%(214/233) of respondents who had heard of rabies said they would seek medical care if they were bitten by a dog. 24%(60/250) of respondents recalled that they or another household member had been bitten by a dog since 2005 and of those, 83% (50/60) sought medical treatment afterwards; 45%(27/60) had sought treatment at the Institut Pasteur du Cambodge (IPC).

Attitudes to interventions: 96%(136/141) of dog-owners surveyed would be willing to vaccinate their dog, 42%(59/141) would be willing to have it spayed and 52%(73/141) castrated.
Conclusions:

The results indicate a high level of awareness of rabies amongst the surveyed population. However respondents were less aware that a canine rabies vaccine exists. Dog-owners were reluctant to sterilize their dogs and this was related to a range of factors such as wanting to breed dogs, and religious and cultural concerns about the appropriateness of sterilization. This indicates that sensitisation would be required if such a programme were to be implemented. More data would also be necessary to accurately assess the combined population of owned and stray dogs.

VWB/VSF-Canada RIACON poster presentation:

Intended and actual stated post-bite behaviour indicates high levels of positive health-promoting behaviour. The proportion of people who sought treatment at the IPC, which provides free post exposure treatment (PET), highlights the important contribution of this service.

A study comparing levels of knowledge and awareness in more rural parts of the country would help to inform a country-level rabies strategy.
Is death in rabies related to specific neuroanatomical pathology? - A study in human, canine and rodent brains

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Rabies retains the distinction of being the infectious disease with the highest case fatality ratio. In spite of many studies in the area of research pertaining to rabies neuropathogenesis numerous questions remains unanswered, especially the pathomechanism of lethality is not known. Under natural conditions the clinical disease does not usually manifest for a varying periods and varying from host to host. The precise location of the virus during that period and its form remains amongst the most puzzling and intriguing aspect of rabies neuropathogenesis. Considering the above facts we tried to probe for consistent neuropathology in the brain during natural infection of humans and canines and experimental infection in mice by virulent street virus and laboratory CVS strain.

In humans and canines following terminal natural infection it is expected that the viral antigen would be global and may not give insight into the progression of the disease. To address this limitation, in a rodent model virulent lab strain of virus was inoculated into mice peripherally and the animal brains were collected at different time points and were examined and compared to the viral load in human and canine brain. The sections from the nervous tissue from human (n= 10), canines (n=10) and mice (n= 6) was immunostained for rabies viral antigen by immunoperoxidase method and the neuroanatomical distribution was mapped. In all the brains, Human, canine and mice there was consistent involvement of thalamus, raphe nuclei and reticular formation in brain stem and vagal nuclei correlating with fatality. In mice, temporally there was a caudocranial spread of the virus from the peripheral nerve, sensory ganglia, spinal cord, brain stem and thalamus. The cerebellar and cerebral involvement was diffuse and did not appear to correlate with mortality. The critical neuroanatomical areas were found involved only
RIACON 2009

PANEL DISCUSSION
Panelists:

*Dr. Betty Dodet (CSRIO Division of Animal Health, Queensland, Australia)*
*Dr. Luninning Villa (ASEAN)*
*Dr. F-X. Meslin, WHO, Geneva*
*Dr. A. Rahman (RIA foundation)*
*Dr. Ong Bee Lee WHO/WPRO*
*Dr. Nguyen Thi Hong Hanh (Vietnam)*
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Moderator:

*Dr. F-X. Meslin, WHO, Geneva*

Reported by:

*Dr. Betty Dodet (CSRIO Division of Animal Health, Queensland, Australia)*

Panel discussion: Gaps and strategy for rabies elimination within region

The panel discussion in the last session of RIACON was moderated by Dr. F-X. Meslin, WHO, Geneva and reported by Dr. Betty Dodet (AREB). Panellists included Dr. A. Rahman (RIA foundation), Dr. Henry Wilde (Thailand), Dr. Luninning Villa (ASEAN), Dr. Nguyen Thi Hong Hanh (Viet Nam), Dr. Ong Bee Lee WHO/WPRO, Dr. F-X. Meslin (WHO), and Dr. Betty Dodet (AREB)
1. Current Rabies Situation in Asia

The estimated number of human rabies deaths in Asia is approximately 30,000-40,000 annually (20,000 in India, 2,000-10,000 in Bangladesh achieved from website at http://bangladesh-animal-care.org. Over 95% of human cases are transmitted by dogs. Rabies free countries (Malaysia, Japan, Australia), spend much efforts to avoid rabies introduction from Asian rabies endemic countries, such as strict control of the dog population and of animal introduction from other countries.

Thailand, Sri Lanka and the Philippines have implemented rabies control programs for more than a decade. These countries have been using cell culture vaccines and have developed ID vaccination regimens. This has resulted in a sharp decrease in human rabies deaths (from 57 in 1998 to 9 in 2008 in Thailand); but rabies is still present (250 human rabies deaths in the Philippines; 50 in Sri Lanka in 2008), since canine rabies is still endemic in some areas of these countries.

The number of human rabies deaths has been increasing heavily in China, peaking at 3,300 cases in 2007, with southern provinces more heavily. Rabies emerged in new territories that were previously rabies-free (Flores 1997, Bali, 2008) when others are becoming provisionally rabies free such as Siquijor, Philippines, and Phuket, Thailand. A WHO-sponsored study is underway in Pakistan to estimate the annual number of rabies deaths.

2. Vaccines

India, Nepal and Vietnam recently discontinued production of nerve tissue vaccine (NTV) and adopted cell-culture vaccines for PEP. India is implementing ID rabies vaccination in some states such as Kerala and Orissa, and launched a pilot projects for prevention and control of rabies in 5 cities.

Sheep brain vaccine is still produced and used (free of charge) in Pakistan, Bangladesh and Myanmar. However cell culture vaccines are available in these countries, and free of charge in a large privately funded hospital in Pakistan.

The recognition of new rabies vaccines which were manufactured in China, India and some other countries should be encouraged to follow the standard international procedures and WHO by evaluating their effectiveness, quality testing and safety. The quality control of new vaccine should be made by outsiders based on that procedure rather than its own company or manufacturers. Many cut off points (alcohol level, dilution...) are different from countries to countries which would be needed to conduct studies on, e.g. the standard procedure for new vaccine evaluation differed from Thailand and Sri Lanka (Dr. Henry Wilde, Thailand).

With about 30,000 human rabies deaths each year in Asia, there is still a big gap between developed and developing countries. Shifting from nerve tissue vaccine (NTV) to cell culture vaccines for PEP, may result in a lower affordability of PEP for the poor. (Dr. Nguyen Thi Hong Hanh, Viet Nam)
3. National Rabies Surveillance, Control and Prevention Program

A National Conference on Rabies will take place in early October in Pakistan, with the participation of the Health Secretary. There is no national rabies surveillance or control program in Cambodia. The Pasteur Institute is the only rabies prevention centre in the country, while rabies prevalence in dogs can be as high as 46%. About 20 000 PEP are annually provided free of charge by the Pasteur Institute.

Even in countries that implemented rabies control programs, human rabies deaths still occur, because of unreported exposures, (especially in children), lack of treatment after exposure or delayed PEP, because of a lack of awareness, or low affordability of PEP. Elimination of human rabies requires control of canine rabies.

4. Progress

a. Global initiatives

The establishment of the Alliance for Rabies Control (ARC) and of a World Rabies Day (WRD) were major achievements for rabies control. Over 100 countries participated in the last WRD, with many initiatives taking place in Asia. The ARC has been active in coordinating partners, to help funding and implementing programs and pilot projects, through the Partners for Rabies Prevention (PRP) Group. PRP is an informal network of stakeholders working in the field of rabies prevention and control (rabies experts form endemic countries, International Organizations, NGOs, and industry).

b. Inter-country cooperation in Asia

Association of Asian Nations
- Involvement of the Association of Southeast Asian Nations: the ASEAN + 3 Countries Initiative (13 countries) developed the resolution of eliminating rabies by 2020, which was adopted by the ASEAN Plus Three Countries (Indonesia, Malaysia, Philippines, Singapore, Thailand, Brunei Darussalam, Viet Nam, Lao PDR, Myanmar, Cambodia, + China, Japan, South Korea).
- India recently adopted in 2009 the resolution of eliminating the rabies by 2020.
- Sri Lanka had already taken the resolution to eliminate rabies by 2016.

Establishment of rabies expert networks
- The Asian Rabies Expert Bureau (AREB), an active network established in 2004 that meets on an annual basis.
- The Rabies in Asia (RIA) Foundation (with chapters in various Asian countries), established in 2007 established in 2007, organizes biennial meetings.

c. Pilot projects and public-private cooperation

- PrEP vaccination of schoolchildren: pilot project in Cabusao, Camarines Sur, Philippines;
WHO coordinated project aiming at the elimination of canine rabies in Visayas Islands (Philippines). This project is funded by the Bill & Melinda Gates Foundation (10 million US$);

Bohol Rabies Prevention and Eradication Program, a cooperative effort of the ARC, WHO, the Philippines Government and a Private Foundation, with community involvement for canine rabies control.

5. Challenges and Components of Strategy for Rabies Control and Elimination

a. Comprehensive programs have been implemented, including

- Affordable PEP (including RIG for category III exposures);
- PrEP of most at risk (children) in endemic countries. Several studies carried out in Thailand, India and Viet Nam confirmed the effectiveness of rabies PrEP in infants or schoolchildren.
- Canine rabies was also controlled at the same time by:
  - Vaccination – high coverage to be obtained;
  - Responsible dog ownership;
  - Human dog population control.

b. Challenges and Components of Strategy for Rabies Control and Elimination

South America, Europe, Korea, Singapore, Malaysia and Japan succeeded in controlling rabies thanks to strong government actions, including legislation and law enforcement. Governments should be strongly encouraged to bring down the number of human rabies cases firstly through dog control, but also through post-exposure vaccination and pre-exposure vaccination (PrEP); effectiveness of (PrEP) is, however still to be demonstrated (Dr. Henry Wilde, Thailand).

For animal control, more support should be obtained from governments, NGOs and other organizations, especially for dog population control and dog vaccination by indirect or direct methods. Involvement of local authorities and local governments in rabies control and prevention should be increased. (Dr. Ong Bee Lee WHO/WPRO).

Remarkable achievements and progress in rabies control, availability of high quality vaccines, and implementation of effective vaccination programs should be acknowledged. But in many parts of the world, there is a lack of cooperation between veterinary and public health/medical services. For example, dog culling is prohibited by law in India. Closer inter-sectoral cooperation is necessary to build-up control programs, one the most important component of which is education about rabies (Dr. A. Rahman, RIA foundation).

The ASEAN+ 3 countries adopted the resolution to prevent and control rabies, with the goal of rabies elimination by year 2020. In order to reach this goal, a roadmap must be established, and yearly achievements must be defined, with the specific resources, actions and contributions requested from every regional organization. Possible donors must also be identified. ASEAN+ 3 set a strategic framework and calls for action in a series of meetings. However, the ASEAN+3 countries have different needs because of different
levels of development. Thus, all organizations, WHO, OIE, and ASEAN should put more effort to help countries in terms of rabies control and prevention. So we need clearly defining of who in charge, resources. Clear actions should be designed at national and regional levels; resources necessary for their implementation should be defined, and those in charge should be clearly designated (Dr. Luninning Villa, ASEAN).

Progress in rabies control and prevention activities has been much slower in Bangladesh, where the nerve tissue vaccine is still used. However, switching to cell-culture vaccines has been planned, and the country is seeking international support and assistance, e.g. for guidelines (Dr. Abdul Hannan, Bangladesh).

While the emergence of **Avian Influenza (H5N1)** and other new **zoonoses** in Asia diverts the attention of governments and the international community from other less visible endemic zoonotic diseases which like rabies have a significant health and economical burden, it is necessary to make profit of any opportunity to advocate for rabies control activities. (Dr. F-X. Meslin, WHO, Geneva).

**c. Success in rabies control requires**

- Political will and involvement
- Population/communities information and participation
- Financial support: private-public partnerships.

**6. What do we need in the future for rabies control and elimination?**

Although it is important to have ambitious goals, more focus should be placed on a roadmap with more realistic targets, that can be met in the near future (Dr. Hervé Bourhy, France).

Recent studies revealed that rabies is a heavy burden for both the public health and the economy of the countries. This is significant evidence to attract the attention from government and different sectors and convinced them to take actions against rabies, e.g. in Viet Nam. Inter-sectoral collaboration plays a very crucial role in rabies control (Mr. Nguyen Viet Hung, Viet Nam).

Rabies control and elimination represents a tremendous challenge; and many obstacles need to be overcome. In ASEAN context, we should proceed step by step, with defined milestones, starting with smaller projects and progressing to larger initiatives: setting up a surveillance system, evaluating the disease burden, advocating for rabies control, and implementing rabies control projects, beginning in defined areas, for instance in touristic areas, as part of an healthy tourism initiative (Dr. Luninning Villa, ASEAN).
RESOLUTION


THE PARTICIPANTS from medical and veterinary services from 13 rabies infected and rabies free Asian countries plus Australia in the 2nd RIA International Conference on Rabies in Asia held in Hanoi, Viet Nam on 9-11 September 2009 and organized by NIHE/RIA Vietnam Chapter in collaboration with the EID program of the ASEAN +3

1. Recognizing the burden rabies represent in their countries, where altogether about 30,000 people die of rabies annually with at least 40% of these deaths are among children less than 15 years of age;

2. Knowing that the presence of the disease in most Asia countries leads to an estimated 10 million post-exposure prophylaxis (PEP) regimens in humans as well as millions of preventive immunization in animals thus making rabies a significant and continuously increasing economic burden particularly for the national health and agriculture sectors;

3. Noting that human and dog rabies during the past years has been spreading in Asia to historically rabies-free areas particularly islands and re-emerging in countries where it had been previously brought under control;

4. Acknowledging the limited resources and low inter-sectoral collaboration for rabies control in human and animal in many Asian countries in spite of some progress made in dealing with other diseases of animal origin;

5. Welcoming the progress reported by many Asian countries in their efforts to control human rabies through discontinuation of local production of animal brain derived vaccines for human PEP and procurement of larger quantities of modern cell culture vaccines to improve their country-wide availability;

6. Convinced of the efficacy of mass vaccination of dogs for rabies control and elimination and the need for concomitant strengthening of community based activities for long term dog population management;

7. Supporting the efforts made by an increasing number of Asian countries to tackle the problem in their dog population and noting promising results obtained in some of them;

8. Recognizing the usefulness of intradermal PEP regimens, when properly administered using vaccines that have demonstrated their immunogenicity by this route in clinical trials, to reduce costs and increase vaccine availability as well as the added protection that preventive immunization provides to certain human age group particularly children most at risk of rabies;
9. Aware that political commitment and action at the highest level of all Asian rabies- infected as well as rabies-free countries is necessary to mobilize required resources for human and animal health services;

10. Gratefully acknowledging the support of the Gates Foundation and WHO to field demonstration projects for prevention of human rabies through dog rabies elimination in Africa and Asia whose results will be used to stimulate similar programme;

11. Taking note of the "Call for Action towards the elimination of Rabies in ASEAN Member States and the plus three countries" developed by the ASEAN Plus Three Emerging Infectious Diseases Programme /AusAID/NIHE meeting on Strengthening cooperation & information sharing on rabies held in Ha Long Vietnam in April 2008 and thereafter endorsed by Health and Agriculture Ministers meetings.

12. Acknowledging the facilitating and supporting role that WHO, OIE, Food and Agriculture Organization (FAO), the ASEAN, SAARC and other relevant institutions such as the Gates Foundation, Alliance for rabies control, Asian Rabies Expert Bureau and ICAM (International Campanion Animal Management) play in zoonoses control and human and animal rabies control and elimination in particular are committed to working together to meeting the goal towards eliminating human and dog rabies in Asia by 2020.

HEREBY RECOMMEND the following: Here compilation of the conclusions and recommendations from the various sessions (on the basis of the report of Chairs/co-chairs/Rapporteurs):

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<th>Session 1:</th>
<th>Rabies Situation (advances and setbacks) (Rapporteurs M.K. Sudarshan, B. Dodet, R. Deray and L.Villa)</th>
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<td>Session 2.1:</td>
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<td>Animal rabies control (Rapporteur S. Lapiz assisted by S.Vallentine and F.X. Meslin)</td>
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<td>Session 3.1:</td>
<td>Fundamental and applied research (Rapporteur R.Frank assisted by H.Bourhy)</td>
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<td>Session 3.2:</td>
<td>Burden of rabies studies (Rapporteur R.Franka assisted by A.Khan and S. Vong)</td>
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AND TO THIS END, the Participants in this Symposium RESOLVED TO take 7 steps to reach the goal of human and dog rabies elimination by 2020 by

(1) advocating for rabies prevention and control at all levels of the society and make the best use of the World Rabies Day to mobilize people, government, decision makers, funding organizations and other resources on the subject

(2) strengthening activities for the surveillance of rabies in humans and animals to better assess the burden of rabies and identify rabies hot spots;

(3) developing, reviewing if already ongoing and, if necessary, redirecting national plan for rabies control towards intensified control of the disease in its animal reservoir and by first targeting high risk areas and expanding to other areas in a progressive manner to finally reach the goal of human rabies elimination;

(4) discontinuing in the few Asian countries where they are still in use the administration of nervous tissue vaccines and taking measures to ensure availability and affordability of safe and efficacious modern rabies biologicals (vaccines and immunoglobulins)

(5) (4bis) ensuring the compliance to human rabies prophylaxis nationals or WHO guidelines, by enhancing communication on the need to complete the vaccination schedules and on the compulsory use of rabies immunoglobulins in severe exposure cases (grade III)

(6) considering in countries where there is no shortage of vaccine Pre-exposure prophylaxis vaccination of infants and children, by studying the feasibility of incorporating rabies vaccine into pre-exposure (PrEP) universal immunization programme for infants and/or schoolchildren;

(7) requesting through appropriate channels the WHO Regional Committees of the South- East Asia Region (SEAR) and the Western Pacific Region (WPR) to reinforce respective Regional Office's capabilities to meet the demands from Member States for technical assistance, technology transfer and the launching of regional initiatives for dog rabies control and elimination in Asia in close collaboration with the ASEAN and SAARC.

SUBMIT this RESOLUTION for consideration by their respective Ministers of Health and Agriculture as well as national, regional and global as well as donor agencies.
CLOSING SPEECH

Asso. Prof. Nguyen Tran Hien
Director National Institute of Hygiene and Epidemiology
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After three days of hard working, we are happy to say that the objectives of the conference have been achieved. One hundred and forty seven participants from 31 countries and International organizations, agencies, institutions from both government and non-governments have attended The 2nd meeting RIACON 2009, VIET NAM CHAPTER.

During last three days, we have heard 45 excellent presentations focusing on the updated rabies diagnosis, practices in human and animal rabies control and prevention in ASIA countries and sub-continents. We all agreed that rabies remains a challenging health problem and the road is still long. It still faces to less attention from local authorities, to lack of resources and inter-sector collaboration. All country-reports and documents have been well prepared beforehand and clearly presented during the conference. Many creative and realistic discussions were actively raised by the speakers and advisors. We have learned and shared with each other the valuable experiences, data and information from the country and scientific reports as well. The most updated strategies, policies and recommendation of effective rabies control and prevention methods as well as the diagnoses and application of conventional laboratory diagnosis were also discussed during the conference. They are really beneficial to all of us and then in turn help to promote rabies control program in our region.

We do believe that the WHO, Rabies in Asia Foundation, Companies will continue to collaborate and support rabies research, control and prevention in the ASIA countries. The Colleagues of all country members and scientists will keep in touch, and continue to share your successes, experience in the future.

I do hope that you have had a good time and pleasure during the conference and staying in our country. On behalf of the National Institute of Hygiene and Epidemiology, Ministry of Health of Vietnam, once again I would like to express our sincere thanks to the WHO, Rabies in Asia Foundation; Sanoffi Pasteur, Novartis Vaccines Companies and all distinguished guests, speakers, and participants for your precious contributions to the success of the conference.

I am particularly thankful to the Organizing Committee, Secretariat for their excellence arrangement and support for the Conference. I wish you all good health and good trip back home. I would like to declare closing the Conference.

Thank you.
ANNEX 1. LIST OF SPEAKERS AND PARTICIPANTS

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88. Dr. Prinya Sirlkupt

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94. Mrs. Doreen McGrath
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    Vice Minister, Ministry of Health, Viet Nam

96. Dr. Nguyen Van Binh
    Ministry of Health, Viet Nam

97. Dr. Tran Thanh Duong
    Ministry of Health. Ha Noi, Viet Nam

98. Dr. Phan Trong Lan
    Ministry of Health. Ha Noi, Viet Nam

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    Section of Diagnosis, Division of Animal Health, Ho Chi Minh city

110. Dr. Huynh Huu Loi
    Division of Animal Health, Ho Chi Minh

111. Dr. Vien Quang Mai
    Deputy Director, Nha Trang Pasteur Institute

112. Dr. Pham Quoc Bao
    Director of Gia Lai preventive medicine center
113. Dr. Van Dang Ky  
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117. Mr. Nguyen Manh Ha  
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118. Dr. Ngo Chau Giang  
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119. Dr. Nguyen Vinh Dong  
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123. Dr. Do Phuong Loan  
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124. Ms. Nguyen Hong Trang  
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125. Dr. Nguyen Cong Khanh  
National Institute of Hygiene and Epidemiology

126. Mrs. Nguyen Thi Van

127. Hoang Minh Hien,  
VABIOTECH
ANNEX 2. ORGANIZING COMMITTEE

Chair person
Dr. Nguyen Thi Hong Hanh
Deputy Director, National Institute of Hygiene and Epidemiology
RIA, Vietnam chapter

Scientific Committee
Dr. M.K. Sudarshan
President, Rabies in Asia Foundation, India

Dr. S.N. Madhusudana
Vice President, Rabies in Asia Foundation, India

Advisors
Dr. F.X. Meslin
Team Leader - Neglected Zoonotic Diseases (NZD)
Office of the Director, Department of Neglected Tropical Diseases (NTD)
Cluster HIV/AIDS, Malaria, Tuberculosis and Neglected Tropical Diseases (HTM) WHO Headquarters, Geneva Switzerland.

Dr. Gongal
Invited by could not attended

Dr. B.J. Mahendra
Executive Director, RIA Foundation

Dr. Trinh Quan Huan
Vice Minister, Ministry of Health, Vietnam

Dr. Nguyen Tran Hien
Director, National Institute of Hygiene and Epidemiology, Hanoi, Vietnam

Dr. Luninning Villa
Programme Facilitator, ASEAN Plus Three EID Programme Phase II. Health and Population Unit, Bureau for Resources Development, ASEAN Secretariat

Dr. Khin Devi Aung
Programme Facilitator, ASEAN Plus Three EID Programme Phase II. Health and Population Unit, Bureau for Resources Development, ASEAN Secretariat
ANNEX 3 THE SECOND RIACON SECRETARIAT

Dr. Nguyen Thi Kieu Anh
Virology Department,
National Institute of Hygiene and Epidemiology, Hanoi, Vietnam (NIHE)

Dr. Tham Chi Dung
International Cooperation Department,
NIHE

Dr. Le Phuong Mai
Department of Community Health and Network Coordination,
NIHE

Dr. Nguyen Vinh Dong
Virology Department,
NIHE

Dr. Nguyen Tuyet Thu
Virology Department,
NIHE

Mr. Nguyen Thai Bang
Department of Informatic Technology,
NIHE

Ms. Nguyen Hong Trang
Department of International Cooperation,
NIHE
ANNEX 4. CONFERENCE PROGRAM

Day 1 (09 September)

Opening session

08:00 - 09:30  Inauguration
Release of RIA Foundation video film
Disease on "Rabies - A fatal but preventable

Session 1: Overview of rabies in Asia Country and sub-continent reports

Chair person: Dr. M.K. Sudarshan, President, Rabies in Asia Foundation, India
Co-Chair person: Dr. M.K. Sudarshan
Report by: Prof. Dr. Quing Tang, CDC China

09:30 - 10:00  Rabies Rabies in Asia: Evolution of the situation since the Asian Rabies meeting, Hanoi 2001
Dr. Betty Dodet, Representative of AREB

10:00 - 10:30  Call for Action and Advocacy strategy "towards the elimination of rabies" in ASEAN +3 countries
Dr. Luningning Villa, Programme Facilitator
ASEAN Secretariat
Health and Population Unit, Bureau for Resources
Development
ASEAN Plus Three EID Programme Phase II

10:30 - 11:00  Rabies Program in Brazil
Dr. Marcelo Wada, Ministry of Public Health, Brazil
National Rabies Control Brazil

11:00 - 11:30  Rabies Research: Current Challenges and Future Approaches
Dr. Franka Richard (CDC/CCID/NCZVED
Centers for Disease Control and Prevention, US
Vector-borne, and Enteric Diseases
Rabies Program National Center for Zoonotic

Rabies in North-Eastern Asian countries (15 minutes each)

Chair person: Dr. F.X. Meslin, World health organization
Co-Chair person: Dr. Betty Dodet
Report by: Dr. Betty Dodet, Representative of AREB

11:30 - 11:45  Rabies in China
Dr. Quing Tang
Institute for Viral Disease Control and Prevention, Chinese Center for Disease Control and Prevention, Head of Rabies Section
Rabies in South-Western Asia (15 minutes each)

Chair person: Assoc. Prof. Nguyen Tran Hien, Director, NIHE
Co-Chair person: Dr. Raffy Deray, National Rabies Focal Point, Philippines
Report by: Dr. Raffy Deray

13:30 - 13:45 Rabies in Pakistan
Dr. Naseem Salahuddin
Dept. of Infectious Disease, The Indus Hospital
Pakistan

13:45 - 14:00 Rabies in Nepal
Dr. DD Joshi
Director, National Zoonoses and Food Hygiene Center, Kathmandu, Nepal

14:00 - 14:15 Rabies in Sri Lanka
Dr. PAL. Harischandra
Director, Public health Veterinary Services
Ministry of Healthcare & Nutrition, Sri Lanka

14:15 - 14:30 Rabies in Bangladesh
Dr. Shafiqur Rahman
Research (IEDCR), Bangladesh
Institute of Epidemiology, Disease Control &

14:30 - 14:45 Rabies in India
Dr. M.K. Sudarshan
President, RIA Foundation, KIMS, Bangalore

Rabies in South-Eastern Asia and other Regions (15 minutes each)

Chair person: Dr. Luningning Villa
Co-Chair person: Dr. Luningning Villa, Programme Facilitator, ASEAN Plus Three EID Programme
Report by: Dr. Chris Morrissy, CSIRO Livestock Industries, Australia

15:00 - 15:15 Rabies in the Philippines
Dr. Raffy Deray
Control Department of Health, Manila
National Center for Disease, Prevention and National Rabies Focal Point, Philippines

15:15 - 15:30 Rabies in Thailand
Dr. Pranee Panichabongse
Director of Zoonoses Control Subdivision
Bureau of Animal Disease Control and Veterinary
Ministry of Agriculture and Cooperatives, Thailand

15:30 - 15:45 Rabies in Vietnam
Dr. Nguyen Tran Hien
Director of National Institute of Hygiene and Epidemiology, Hanoi, Vietnam
15:45 - 16:00  Rabies in Australia  Dr. Chris Morrissy  Scientific Coordinator AAHL Regional, Program; Response CSIRO Livestock Industries, Australia

16:00 – 16:15  Rabies in Bhutan  Dr. Karma Rinzin  Program Director, National Center for Animal Health, Bhutan

16:15 – 16:30  Rabies in Mongolia  Dr. Baatar Undraa, Deputy Director of the National Center for Infectious Diseases, Mongolia

16:30 - 17:30  Discussion and Wrap-up Session 1

Day 2 (10 September)

Session 2: Update practices in human and animal rabies surveillance, prevention and control

Update on human rabies prevention

Chair person: Dr. S.N. Madhusudana, NIMHANS, Bangalore  
Co-Chair person: Dr. B. Quimbao

Report by: Dr. B. Quiambao, RITM, Alabang, the Philippines

08:30 - 08:45  New developments and controversies in rabies  Dr. Henry Wilde  Chulalongkorn University, Thailand

08:45 - 09:00  Assessing the relationship between antigenicity & meta- analysis administered by intradermal route: Results of a immunogenicity of human rabies vaccines when administered by intradermal route: Results of a meta- analysis  Dr. Ravish H.S  KIMS, Bangalore, India  Department of Community Medicine

09:00 - 09:15  Providing booster in one day using 4-site intradermal vaccination  Dr. Prapiporn  Shantavasinkul Queen Saovabha Memorial Institute The Thai Red Cross Society, Thailand

09:15 - 09:30  Replacing nervous tissue vaccines by modern cell culture vaccines: lessons learnt  Dr. B. Quiambao  RITM, Alabang, the Philippines
Pre-exposure children and population at risk. When should it be implemented?

Dr. Raffy Deray
National rabies focal point
Manila, the Philippines

Immunogenicity, booster response and safety of purified chick embryo cell rabies vaccine administered intramuscularly or intradermally to 12-to 18-month-old Thai children, concomitantly with Japanese encephalitis vaccine

Dr. Kriengsak Limkittikul
Department of Tropical Pediatrics
Faculty of Tropical Medicine, Mahidol University, Rajvithi Rd, Phayathai, Thailand

Rabies Pre-exposure Prophylaxis in Children: Anamnestic immune response to PCECV booster doses up to 5 years after primary vaccination

Dr. Thavatchai Kamoltham
Office of Permanent Secretary, Ministry of Public Health, Tivanond Road, Thailand.

Update on Rabies Surveillance and Epidemiology

Chair person: Dr. Ong Bee Lee WHO/WPRO
Co-Chair person: Dr. Stella Marie D. Lapiz, DVM, Provincial Veterinarian, Provincial Government of Bohol
Report by: Dr. Stella Marie D. Lapiz

Best practices in laboratory diagnostic and surveillance of rabies

Dr. S.N. Madhusudana
NIMHANS, Bangalore

Update on Animal Rabies Control

Dog population management and rabies control. How to overcome the challenges?

Dr. Sarah Vallentine and Dr. A. Rahman
1 World Society for the Protection of Animals, Thailand office.
2 Vice-President, RIA Foundation & Secretary-Commonwealth Veterinary Association (CVA), Bangalore

Community-based rabies control project: How far should we go?

Dr. Stella Marie D. Lapiz
DVM, Provincial Veterinarian
Provincial Government of Bohol

Dog rabies control in Sri Lanka

Dr. PAL. Harishchandra
Director, Public Health Veterinary Services, Ministry of
<table>
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<tr>
<th>Time</th>
<th>Session Title</th>
<th>Speaker/Institution</th>
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<td>12:15</td>
<td>Discussion and wrap-up session 2</td>
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<td>12:30</td>
<td>Lunch Break</td>
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**Session 3: Fundamental and Epidemiological Research**

*Chair person:* Dr. Franka Richard, Centers for Disease Control and Prevention, US  
*Co-Chair person:* Dr. Herve Bourhy, Pasteur Institute, Paris  
*Report by:* Dr. Franka Richard

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<tr>
<td>13:30</td>
<td>New and future developments in rabies laboratory diagnosis</td>
<td>Dr. Herve Bourhy, Pasteur in Paris</td>
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<td>13:45</td>
<td>Monoclonal antibody for PEP: current status of research</td>
<td>Dr. Franka Richard, Rabies Program National, CDC, USA</td>
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<td>14:15</td>
<td>Development of CL184 human monoclonal antibody cocktail for rabies post-exposure prophylaxis, from preclinical design to clinical evaluation</td>
<td>Dr. Lex Bakker, Crucell Holland B.V</td>
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<td>14:45</td>
<td>Bat Lyssaviruses epidemiology in Australasia: evaluating its current and potential public health implications?</td>
<td>Dr. Chris Morrissy, Scientific Coordinator, AAHL Regional Program, CSIRO Livestock Industries, Australi</td>
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<td>15:15</td>
<td>Coffee break</td>
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<td>15:30</td>
<td>Lyssavirus pathogenesis, host immune response and human disease therapy</td>
<td>Dr. Thiravat Hemachuda, Chulalongkorn University, Bangko</td>
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<td>15:50</td>
<td>Site of entry of the rabies virus from the nose and oral cavity; and new methods of treatment of rabies using olfactory mucosa and by breaking BBB</td>
<td>Dr. Totada R. Shantha, Director, Integrated Medical Specialists, IPTMD,COM, 3 E-Technology Inc</td>
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<tr>
<td>16:20</td>
<td>Recent developments in understanding human rabies using animal models</td>
<td>Dr. Alan C. Jackson, Professor and Head Section of Neurology University of Manitoba Health Sciences Centre</td>
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Healthcare & Nutrition, Sri Lanka
### Assessing the Burden of Rabies through an Epidemiological Survey: Challenges and Opportunities

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<tr>
<td>16:50 - 17:10</td>
<td>Pakistan</td>
<td>Dr. Aamir Khan, Pakistan</td>
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<td>17:10 - 17:30</td>
<td>Cambodia</td>
<td>Dr. Sirenda Vong et al</td>
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<td>17:30 - 18:00</td>
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<td>Discussion and wrap-up session 3</td>
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Day 3 (11 September)

Session 4. Scientific and advanced research

Chair person: Alan C. Jackson, MD, FRCPC, Professor and Head, Section of Neurology, University of Manitoba, Health Sciences Centre, Winnipeg, Manitoba, Canada
Co-Chair person: Dr. B J Mahendra, Executive Director, RIA Foundation
Report by: Dr. B J Mahendra

08:30 - 08:40
Guillain Barre syndrome Versus Paralytic rabies - at the spinal level
Dr. Anita Mahadevan
Department of Neuropathology, National Institute of Mental Health & Neurosciences, Bangalore, India

08:40 - 08:50
IDRV- Kerala Experience
Dr. Thomas Mathew
Department of Community Medicine, TD Medical College, Alappuzha, Kerala, India

08:50 - 09:00
Challenges in IDRV
Dr. Durga Madhab Satapathy
Associate Professor
Department of Community Medicine, M.K.C.G. Medical College, Berhampur, Orissa

09:00 - 09:15
An overview of clinical trials with Purified Duck Embryo vaccine (PDEV): Indian Experiences
Dr. D.H. Ashwath Narayana
Department of Community Medicine, KIMS, Bangalore, India

Poster presentations with authors

09:15 - 09:45
Molecular characterization of the complete genome of a rabies virus isolate from India
Dr. Anita Mahadevan
Department of Neuropathology, National Institute of Mental Health & Neurosciences, Bangalore, India

Comparative evaluation of human embryonic kidney cell line (HEK293) and neuro 2a and BHK 21 cell lines for rapid isolation of street and field rabies viruses
Dr. Padinjaremmattathil
Thankappan Ullas Department of Neurovirology, NIMHANS, Bangalore

Comparative evaluation of a newly developed direct rapid histochemical test (dRIT) and fluorescent antibody technique (FAT) for rapid diagnosis of rabies in animals and humans
Dr. Subha Sundramoorthy
Department of Neurovirology, NIMHANS, Bangalore, India
Is death in rabies related to specific neuroanatomical pathology? - A study in human, canine and rodent brains

Assessing awareness of rabies characteristics and prevention in Cambodia

Enabling Rabies Post-Exposure Prophylaxis in India: Intradermal Vaccination Devices

09:45 - 10:00 Coffee break

10:00 - 10:50 Panel discussion

Gaps and strategy for rabies elimination within region

Developing a Resolution on Rabies Prevention and Control and a Press Release

Panelists:

- Dr. Betty Dodet (CSRIO Division of Animal Health, Queensland, Australia)
- Dr. Luninning Villa (ASEAN)
- Dr. F-X. Meslin, WHO, Geneva
- Dr. A. Rahman (RIA foundation)
- Dr. Ong Bee Lee WHO/WPRO
- Dr. Nguyen Thi Hong Hanh (Vietnam)
- Dr. Henry Wilde (Thailand)

Moderator: Dr. F-X. Meslin, WHO, Geneva

Reported by: Dr. Betty Dodet (CSRIO Division of Animal Health, Queensland, Australia)

10:50 - 11:00 Conclusion and recommendations

11:00 - 11:15 Honoring and Closing Session

11:15 - 11:45 RIA Official Meeting

11:45 - 13:00 Lunch break

END OF THE CONFERENCE