RIAICON 2007
First International Conference of Rabies in Asia (RIA) Foundation
3rd - 4th March, 2007
Bangalore, India

CONFERENCE PROCEEDINGS

Compiled and Edited by:
Dr. S. N. Madhusudana
RIACON 2007

First International Conference of Rabies in Asia (RIA) Foundation

3 - 4 March 2007

Convention Centre
National Institute of Mental Health and Neurosciences (NIMHANS)
Bangalore, India

CONFERENCE PROCEEDINGS

Compiled and Edited by:

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Dr. H. Bourhy, France
Dr. Alexander Wandeler, Canada
Dr. R. L. Ichhpujani, India
Dr. Henry Wilde, Thailand
Dr. T. Hemachuda, Thailand
Dr. V. Ravi, India
At the outset let me offer my sincere apologies to all of you for the delay in bringing out this conference proceedings. This was mainly because of my prior commitments both official and personal. The first international conference of RIA, RIACON 2007, which was organized at the convention center, NIMHANS during March 3-4 was a reasonably successful event. The main objective of the conference was to bring together key rabies experts from different Asian countries on a common platform and have them interact mutually and with rabies experts from America and Europe in order to find ways to reduce the burden of human and animal rabies in Asian countries which accounts for 80% of global rabies deaths. Nearly 100 delegates from different Asian countries, USA, Canada, France, UK and Germany participated in this 2-day event. The World Health Organization was represented by Dr. F.-X. Meslin, Co-ordinator, Animal and Food related diseases, WHO, Geneva. Scientific sessions were devoted to rabies situation and on going control efforts from individual countries, the present trends in rabies research in Asia, America and Europe and possible collaboration between the countries. On the second day opportunity was given to presentations from young scientists to discuss their research findings. Special focus was given to the current status of oral rabies vaccination for dogs. The conference ended with a enlightening panel discussion moderated by Deborah Briggs from Kansas State University, USA. The panel discussion emphasized among other things, the need for increasing rabies awareness among both public and policy makers, to prioritize rabies prevention and control measures in their respective countries and to formulate a national rabies prevention and control programmes in countries where it is presently not operational. At the end, the participants of the conference unanimously brought out certain recommendations for the national authorities to implement in their own countries which should eventually reduce the burden of human and animal rabies, if not completely eliminate it. With this scientific event, we feel that a beginning has been made and we look forward for continued interaction and collaboration from all the Asian countries so that we can work together and eventually make rabies a history.

I take this opportunity to thank Dr. D. Nagaraja, Director, NIMHANS, who has always been encouraging my rabies-related endeavours, Dr. V. Ravi, Dr. Anita Desai and other staff members of Department of Neurovirology who helped me in organizing this International Conference. Also, I thank all my students who have helped me in preparing this Conference Proceedings.

Finally, I thank all the sponsors of the Conference, Novartis Vaccines, Sanofi Pasteur, Bharat Biotech International Limited, Sanofi Aventis, Zydus Alidac for their financial support and encouragement for the successful organization of the conference.

Bangalore  
15-12-2007  

Dr. S.N. Madhusudana  
Chairman, RIA
The first conference of Rabies in Asia (RIA) Foundation, RIACON 2007, which was held during March 3 and 4, 2007 at the convention center, National Institute of Mental Health and Neurosciences (NIMHANS), Bangalore, India was a successful event bringing together rabies experts of Asia, Europe and America. The two-day event gave ample opportunity for the experts to interact, exchange scientific information and deliberate on the future strategies for the control and ultimate elimination of rabies from Asian countries. At the end, conclusions and recommendations were formulated by the experts which will be put before the respective country governments for its perusal and action.

On the whole, the conference was successful in highlighting the present rabies situation in Asian countries and the problems that are being faced for its control. It also gave platform to young scientists to share their research findings which I am sure will go a long way to develop future strategies for rabies control. The proceedings of the conference are now ready in a book and CD format. It will also be available on the website of the foundation www.rabiesinasia.org. For reasons beyond our control, the preparation of the proceedings was delayed and we sincerely regret the same. I hope that this publication will act as a source of reference not only for the participants of the conference but also to others working in the field of rabies.

I take this opportunity to thank all the participants and invited speakers of the conference and Dr.D.Nagaraja, Director & Vice-chancellor, NIMHANS for supporting the RIA foundation in its endeavors and for providing the convention centre for the conference. Dr. S. N. Madhusudana, chairman of RIACON, and his colleagues from NIMHANS need to be congratulated for bringing out this publication. The RIA foundation is grateful to Dr. F.-X. Meslin from WHO for his cooperation, advice and support to organization of the event. Lastly, I express my sincere thanks to the sponsors from the industry viz., Sanofi Pasteur, Novartis, Zydis Alidac, Bharat Biotech, Human Biologicals and Sanofi Aventis without whose generous financial grants, this event would not have been possible.

Bangalore, India

18th December, 2007

Prof. Dr. M. K. Sudarshan
President, RIA Foundation
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LIST OF SPEAKERS

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27. Dr. Shailesh Mehta
    Medical Director
    Sanofi Pasteur, India
PROGRAMME

DAY I

8.30 - 9 AM  Registration
9 - 9.30 AM  Inauguration
9.30 - 9.45 AM  Introducing RIA & its Objectives
   Dr. M. K. Sudarshan, India
9.45 - 1.30 PM  Scientific Session I: Reassessing the problem and finding solutions

9.45 - 10.15 AM  Rabies in Asia: Current scene and WHO's Role in control
   Dr. F.-X. Meslin, WHO, Geneva
10.15 - 10.30 AM  Tea/Coffee

10.30 - 10.50 AM  Rabies in India: The present scene and control efforts
   Dr. R. L. Ichhpujani, India
10.50 - 11.10 AM  Rabies in Thailand: The success story
   Dr. K. Thavachai, Thailand
11.10 - 11.30 AM  Rabies in Sri Lanka: Is elimination foreseen?
   Dr. Omala Wimalaratne, Sri Lanka
11.30 - 11.50 AM  Rabies in Philippines: Lessons Learned
   Dr. B. Quiambao, Philippines
11.50 - 12.10 PM  Rabies in Pakistan: New Initiatives
   Dr. Naseem Salahuddin, Pakistan
12.10 - 12.30 PM  Rabies in China: The Resurgence
   Dr. Yong-Zhen Zhang, China
12.50 - 1.10 PM  Rabies in Nepal
   Dr. D. D. Joshi, Nepal
1.10 - 1.30 PM  Rabies Control: Role of NGOs
   Dr. B. J. Mahendra, India
1.30 - 2.15 PM  Lunch

2.15 - 5 PM  Scientific Session II: Rabies Research: Where are we?

2.15 - 2.30 PM  Rabies Research in India: The current scene
   Dr. S. N. Madhusudana, India
2.30 - 2.45 PM  Rabies Research in Thailand: The past and the present
   Dr. Henry Wilde, Thailand
2.45 - 3.15 PM  Rabies Therapy
   Dr. Alan C. Jackson, Canada
3.15 - 3.30 PM  Tea/Coffee
<table>
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<tr>
<th>Time</th>
<th>Event</th>
<th>Speaker</th>
<th>Location</th>
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</table>
| 3.30 - 4 PM  | Rabies Research in Europe  
*Dr. H. Bourhy, France*                          |                             |          |
| 4 - 4.30 PM  | Rabies Research: Collaboration between east and west  
*Dr. D. J. Briggs, USA*                       |                             |          |

**DAY 2**

<table>
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<th>Time</th>
<th>Event</th>
<th>Speaker</th>
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<tr>
<td>9 - 10.30 AM</td>
<td>Scientific session III: Rabies Control: The other side of the coin</td>
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| 9 - 9.20 AM  | Rabies Control: Perspectives from the veterinary side  
*Dr. V. A. Srinivasan, India*                        |                             |          |
| 9.20 - 9.50 AM | Dog Rabies Control in Sri Lanka: Ongoing efforts  
*Dr. P. A. L. Harishchandra, Sri Lanka*     |                             |          |
| 9.50 - 10.10 AM | Oral vaccines for dogs: Present status and future  
*Dr. S. Kilari, India*           |                             |          |
| 10.10 - 10.30 AM | Tea/Coffee                              |                             |          |
| 10.30 - 1 PM | Scientific Session IV: Rabies Prevention in Humans: New Initiatives                        |                             |          |
| 10.30 - 10.50 AM | Implementation of extended PEP in Thailand: Lessons learnt  
*Dr. P. Chantavanitch, Thailand* |                             |          |
| 10.50 - 11.10 AM | Comparative study on the Immunogenicity and safety of PDEV produced in  
India (Vaxirab) and Switzerland (Lyssavac-N)  
*Dr. G. Sampath, India* |                             |          |
| 11.10 - 11.30 AM | Re-exposure realities in rabies prophylaxis  
*Dr. Amlan Goswamy, India*               |                             |          |
| 11.30 - 11.50 AM | Rabies Pre-exposure vaccination in children: A summary of clinical trials  
with PCEC vaccine world wide  
*Dr. Claudius Malerczyk, Germany* |                             |          |
| 11.50 - 12.10 PM | Utility of murine Monoclonal Antibodies for passive Immunotherapy against rabies  
*Dr. K. Muhamuda, India*                |                             |          |
| 12.10 - 12.30 PM | Passive Immunization: Experience with ERIGs produced in India  
*Dr. D. H. Ashwath Narayana, India* |                             |          |
| 12.30 - 12.50 PM | Complete Genome sequence of an Indian isolate of rabies virus  
*Dr. Anita Desai, India*               |                             |          |
| 12.50 - 1.10 PM | Immunogenicity and safety of Indirab: Chromatographically purified Vero cell rabies vaccine  
*Dr. V. Krishna Mohan, India*          |                             |          |
| 1.10 - 1.30 PM | Twenty year clinical experience with Verorab  
*Dr. Shailesh Mehta, India*             |                             |          |
| 1.30 - 2 PM   | Lunch                                      |                             |          |
2 - 3 PM  
PANEL DISCUSSION:  
Reducing Burden of Rabies in Asia: the Challenges ahead  
Moderator: Dr. Deborah Briggs  
Panelists: Dr. F.-X. Meslin, WHO, Geneva  
Dr. Henry Wilde, Thailand  
Dr. R. L. Ichhpujani, India  
Dr. M. K. Sudarshan, India  
Dr. Naseem Salahuddin, Pakistan  
Dr. Yong-Zhen Zhang, China

3 - 3.30 PM  
Conclusions and Recommendations

3.30 - 3.45 PM  
Tea/Coffee

3.45 - 4.30 PM  
RIA Official Meeting
IN AUGURAL CEREMONY

Dr. M. K. Sudarshan, President, RIA welcomed the gathering to the First Meeting of the Rabies in Asia Foundation and expressed hope for fruitful and successful deliberations during the conference. He also expressed thanks to the Director, NIMHANS for giving permission to conduct the conference in the convention center.

Dr. F.-X. Meslin, Coordinator, Animal related diseases, WHO, thanked the Director, NIMHANS and the organizers of the conference. He stressed upon the commitment of the WHO in reducing rabies burden in Asian countries. He said that in recent times some Asian countries have successfully reduced the human rabies deaths while many countries particularly India continues to report thousands of deaths. He expressed happiness over the discontinuation of nerve tissue vaccine in India and hoped that neighboring countries such as Pakistan and Bangladesh will follow suit.

Maj. Gen. Kharb, Chairman of the Animal Welfare Board, released the conference book. Speaking on the state of rabies control in India, he emphasized the need for linking animal welfare activities to human welfare and sustainable development, especially in the rural areas of the country. He pointed out that the number of Animal Birth Control surgeries conducted in the country every year was very less and that there was no attempt on sustained immunization of the operated dogs. He called for novel methods to address the issue and spoke briefly on the newer initiatives such as Oral Rabies Vaccination and Catch, Neuter, Vaccinate and Release strategy. He stressed upon the need for greater involvement of local bodies in the interventions for canine rabies control as it had happened recently in Ahmedabad and expressed hope that rabies control in dogs can be achieved in a humane way.

Delivering the Presidential Address, Dr. D. Nagaraja, Director, said that though the frequency of rabies deaths is much less compared to other infectious diseases, the horrifying nature of the symptoms and eventual death makes it one of the most dreaded diseases known to mankind. He also pointed out the recent happenings in Bangalore and other places in India, where packs of stray dogs mauled some children to death. He wondered about the sudden change in the behavior of stray dogs in recent times. He also stressed upon the need for evolving new strategies for aggressive control of stray dog population and rabies in the country. He also hoped that the recent introduction of oral rabies vaccines for dogs may go a long way in reducing incidence of dog rabies. He expressed hope that the conference would be able to provide guidelines and directions to the government and local bodies in evolving strategies to reduce rabies deaths and eventually eliminate it from Asian countries.

The inaugural ceremony concluded with a vote of thanks from Dr. S. N. Madhusudana, Chairman, RIAcon. He thanked Director, NIMHANS for giving permission to hold the conference. He also thanked all those in the organizing committee for working so hard to make this event possible. He expressed his gratefulness to all the delegates and speakers both at national and international level for participating in the conference and wished them a pleasant stay at Bangalore and hoped that they will have fond memories to carry back home.
Dr. D. Nagaraja, Director, NIMHANS, lighting the lamp during the Inaugural Ceremony.

Dr. S.N. Madhusudana, Chairman, RIACON, lighting the lamp during the Inaugural Ceremony.
Dr. F.-X. Meslin addressing the gathering during the Inaugural Ceremony.

Dignitaries on the dais: From Left to Right: Dr. M. K. Sudarshan, Dr. F.-X. Meslin, Dr. D. Nagaraja, Maj. Gen. Kharb and Dr. S. N. Madhusudana
Globally an estimated 55,000 human rabies deaths occur every year of which 56% is in Asia and 44% in Africa. But rabies continues to remain a neglected disease in both animals and humans. However, the necessary tools for the prevention of human and animal rabies are available. Though WHO, OIE, Rabies in the Americas (RITA), South-East Africa Rabies Group (SEARG) organization and Rabies in Europe (RIE) have been addressing this cause globally and regionally there was a void in Asia as there was no organization in the region to address this issue. To fulfill this long felt need a group of experts from Asia, WHO, CDC and others in a meeting in Mumbai, in December 2005 recommended formation of a body which should urgently work for an expanded and “all inclusive” regional approach to rabies prevention and control in Asia. Subsequently, "Rabies in Asia (RIA) Foundation” was formed and registered as a trust under the Indian Trust Act on 1st April 2006 in Bangalore, India.

The objective of RIA is to bring together the national rabies associations, human and animal health care professionals as well as researchers and government officials throughout Asia to work together with all stakeholders to find regional solutions and strategies for elimination of human and dog rabies in Asia. The country chapters of RIA are formed in India, Pakistan, Sri Lanka, Bangladesh, Thailand, Philippines and China. The first meeting of the RIA foundation is being held as "RIACON 2007" on 3rd and 4th March 2007 at National Institute of Mental Health and Neurosciences, Bangalore, India. About 100 rabies experts and officials from Asia, Europe, and other countries and from WHO and CDC are expected to participate in the deliberations. The theme of the conference is "Reducing rabies burden in Asia - Future perspectives". It is sincerely hoped that the recommendations of the conference is used as a advocacy document to prevail upon national governments to make suitable changes and work for achieving a rabies free Asia. Further details of RIA are available on the website: www.rabiesinasia.org.
RIA – Countries chapters and their chairpersons

1. India - Dr. S.N. Madhusudana, Bangalore.
2. Pakistan - Dr. Naseem Salahuddin, Karachi.
3. Sri Lanka - Dr. PAL Harischandra, Colombo.
4. Philippines - Dr. Beatriz Quiambao, Manila.
5. Thailand - Dr. Prat Boonyawongvirot, Bangkok.

RIA - Advisors

1. Dr. F. X. Meslin - Switzerland
2. Dr. Deborah J. Briggs - USA
3. Dr. Charles E. Rupprecht - USA
4. Dr. Alexander L. Wendeler - Canada
5. Dr. Thiravat Hemachudha - Thailand
6. Dr. Henry Wilde - Thailand
7. Dr. Herve Bourhy - France
8. Dr. R. Lichpujani - India
A recent WHO sponsored study has provided a quantitative prediction of the burden of rabies in Asia with an estimated number of 31,000 rabies deaths representing 56% of the world mortality estimate. Most of those are occurring in India with about 20,000 deaths for this country alone. It is estimated that 80% of the cases are occurring in rural areas. The study estimates that more than 2 billion people in Asia are living in countries/territories where dog rabies still exists and are potentially exposed to rabies. The final estimate of 31,000 deaths a year is still likely to be an underestimate of the total mortality and morbidity caused by rabies in Asia.

The estimated global annual number of PEP provided has increased markedly mostly because of changes occurring in Asia. In 2005 the number of PEP provided in China was reported to be almost 8 million and the size of the potential market for these products to be 10 to 12 million by 2010. Usage of PEP has also changed in India, as already observed at the end of the 80s and accelerated during the second part of the 90s, with a drastic increase of number of modern vaccines - both locally produced and imported - being used essentially by the private market.

The replacement of brain tissue vaccines by modern vaccines (cell culture or embryonated egg vaccines) which started in China in 1989 continues. More and more countries are banning the use of brain tissue vaccines and replacing these products by locally produced and/or imported vaccines. Many countries
especially those whose annual requirements are small or remain inferior to the number that would make the development of autochthonous vaccine production a viable proposition have opted for imports. India and China are the two countries which today have developed and/or acquired cell-culture or embryonated egg rabies vaccine production technology in a sustainable manner.

Most rabies cases occur in untreated cases. In general, more PEP are applied in most rabies infected countries than would be necessary to prevent most human rabies deaths if only bites or contact with truly suspect rabid animals were taken into consideration. In Asia in view of the lack of rabies laboratory and systems for dog brain sampling/shipping as well as dog observation and the large number of offending dogs that are reported to be ownerless, the vast majority (up to 90%) of the persons visiting a rabies PEP center after a bite receives a least one vaccine dose. Most PEP in dog rabies infected areas consist in wound cleansing and disinfection and vaccine administration even in category 3 exposure. In the Philippines only 8% of the total number of PEP administered annually combine both vaccine and immunoglobulin. A few Asian countries such as China, India, the Philippines and Thailand have invested recently in purified equine immunoglobulin production mostly to increase availability at the national level. Only China is exporting some limited quantities of purified ERIG.

Comparatively rabies control in dogs has made little progress. No Asian country has eliminated dog rabies since Malaysia did it in the sixties. Many rabies infected Asian countries organize country-wide annual immunization campaigns. Among the most advanced Thailand and Sri Lanka have had long established programmes for dog immunization. During the last 5 years between 4.5 and 5 million dog have been vaccinated annually in the Thai Kingdom. In Sri Lanka about 800 000 dogs are vaccinated annually. In both cases the immunization coverage remains below 75%. Although the number of positive
cases in dogs has been divided by 7 in 10 years in Thailand dog mediated human cases are still reported in many parts of the country. In addition programmes for the management of the dog population (usually by capture, neutering/spaying and releasing) are still limited in size and impact although there are on the increase in some countries like Sri Lanka, India and Thailand.

WHO has continuously provided technical support to its Asian Member States.

In the human rabies vaccine field: WHO has constantly advocated the discontinuation of Semple type vaccine and promoted the use of cell culture and embryonated egg vaccines. This together with providing the evidence for safe and efficacious use of the intradermal route for post exposure prophylaxis as a way to improve access to modern rabies vaccines in developing countries, has made the shift from brain based to cell culture only rabies vaccines possible in countries such as Sri Lanka, the Philippines and more recently India. Vietnam is currently considering abandoning the production of SMBV. WHO has updated its guidelines for rabies post-exposure treatment (TRS 931, Geneva 2005) as well as its section on recommendations on rabies and travellers health (International travel and health, WHO Geneva 2007). The 56th meeting of the Expert Committee on Biological Standardization in October 2005 revised its recommendations for inactivated rabies vaccine for human use produced in cell substrates and embryonated eggs (ECBS, TRS 2006). In the field of research and development of new human biological WHO has initiated with its network of WHO Collaborating Centres on Rabies a study for the development of a cocktail of monoclonal antibodies for rabies post-exposure prophylaxis.

In the dog rabies control and prevention area: WHO studied with world experts the efficacy and safety of oral vaccines for dogs, defined the conditions of utilization and promoted the use of those considered appropriate in certain countries such as Thailand, India. Oral vaccines are being used in Sri Lanka and will be used in pilot project in India very soon. WHO supported dog population studies aiming at defining certain characteristics of the dog populations of developing countries particularly in Sri Lanka and Nepal for Asia. These study protocols are now used as models for the initiation of new population studies in countries tackling the problem of dog rabies control and elimination such as in Cambodia. WHO supports rabies control projects which comply with animal welfare principles.
Rabies, the most dreadful of all the communicable diseases that a man can get from the animals has been endemic in India (except for islands of Lakshadweep, Andaman and Nicobar which are rabies free) since time immemorial. Though the exact figures are not available even today, it is estimated that around 20,000 (APCRI Report 2004) persons die of this disease every year in India. Overwhelming (95%) mortality and morbidity of this disease is as a result of bite by rabid dogs. The dog population, which was 18.8 million according to the 1982 census, rose to 19.7 million in 1987, and is now estimated to be 25 million. Most of these dogs are unprotected against rabies. Rabies cases are seen throughout the year, almost two thirds of the victims are males and about 40% are children less than 14 years of age. As per APCRI 2004 survey, it is estimated that approximately 17.4 million animal bites occur annually in India. About 1.8 million animal bite cases elect to receive post exposure treatment.
A variety of modern anti-rabies vaccines are available in the country which are produced both in the public and private sectors and are also imported. About 9 million doses of tissue culture vaccines are used in India. A very little quantity of equine anti-rabies sera is used in the country mainly because of high cost, unreliable supply and a general fear among the treating physicians about side effects of antisera. Anti-rabies serum is produced in only one public sector institute in the country.

The use of nervous tissue vaccine for humans has been banned in the country. DCGI has recently approved the use of anti-rabies tissue culture vaccines by intradermal route.

![Currently Available Rabies Vaccines](image)

Table showing rabies vaccine availability in India

However, due to various operational and statutory reasons it has not been widely used as yet. Rabies is not considered a priority disease.

Various constraints in rabies control include inadequate resources, lack of political support, lack of consensus on strategy, weak inter-sectoral coordination, inadequate management structure, lack of public cooperation, prevalence of myths and religious faiths.

To address all these issues, a comprehensive national rabies eradication programme is to be implemented. Efforts are under way in this direction. A pilot project to control rabies in selected cities of India has been approved in the 11th 5 year plan.
Within 25 years, human rabies death rapidly decreased from 370 cases per year in 1980 to 21 cases per year in 2005, because of strong ambition and success of Rabies Eradication Program, NTV replacement with TCV (1993), TRC Economical Intradermal Vaccination (1995) and 5 years strategic plan. Key of success comes from the strategic planning, implementation and evaluation, strong commitment with integration of health parties i.e., many governmental departments, non government organization, local government, politicians, mass media, health volunteers, and communities, under the evidence based on information technology, surveillance system and centralized data need to be done. Ministry of Public Health took good care and increase accessibility of the PET by universal coverage insurance system giving free of charge vaccination. With cooperation of Livestock Department, Ministry of Agriculture took care of dog population control and animal vaccination with vaccine supplied by local government. Ministry of Education increased knowledge, attitude and practice of rabies PEP in school children. The Nerve tissue vaccine (NTV) was removed from Thailand in 1993 and replaced with tissue culture vaccine (TCV). The intradermal route of vaccination was introduced in 1994. A strategic plan of action for control of rabies was envisaged in 1996. All these have made an impact and reduced rabies deaths. A pre-exposure vaccination campaign was conducted in the province of Phetchabun from 1998 onwards and this has completely eliminated human rabies deaths form this province. From 1998 to 2007 not a single rabies death has been reported from this province. In the country as a whole the number of rabies deaths for the past 5 years remains stable .The animal rabies incidence has dropped from 45% in 1994 to 22% in 2005. However, the number of people exposed to dog bites has remained constant over the years. This indicates that there is an urgent need to develop new strategies for dog population control.
Graph showing declining rabies deaths in Thailand

Graph showing zero incidence of human rabies deaths in Phetchabun Province in Thailand after implementation of the rabies elimination project
Sri Lanka is an island in the Indian ocean which has a land extent of 64,000 sq. km. with a population of 20.2 million. Rabies is an endemic disease in the country and dog is the main reservoir for transmission of this fatal disease to humans.

Human rabies is a notifiable disease and there were 68 reported deaths due to rabies in the year 2006. In Sri Lanka, it is estimated that there are 375,000 animal bites annually, out of which 77% are due to apparently healthy animals, 2% sick animals, 9% animals had died subsequently and 12% were unknown.

In 1995, the Ministry Of Health took a policy decision to stop the production of nerve tissue vaccine and since then, only rabies cell culture vaccine is used for post exposure prophylaxis in all hospitals in Sri Lanka. About 200,000 animal bite victims are administered anti rabies post exposure prophylaxis (PEP) annually at present. 50,000 are administered rabies immunoglobulins and anti rabies cell culture vaccine (TCV) for category III exposures and 150,000 are administered rabies vaccine only for all category II exposures. In 1997, WHO recommended economical intradermal (ID) administration of anti rabies TCV was introduced in two teaching hospitals in Colombo and over the years gradually introduced in a phased manner to other hospitals in the country. In 2003, ID regimen was implemented in the whole country. 85% of patients seeking PEP are administered anti rabies TCV intradermaly. Training of staff, close supervision and monitoring and rabies awareness programmes were conducted throughout the island before introduction of the ID regimen. The Ministry Of Health spends over 3 million US dollars for PEP in Sri Lanka, which is offered free of charge to patients in government hospitals.

To reduce wastage of rabies immunoglobulins and TCV and for better management of patients, anti rabies PEP units are established in most major hospitals, manned by specially trained staff. A responsible medical officer is appointed to each unit for better supervision and to give confidence. A 24 hour hotline is made available for health care personnel from any part of the country to obtain expert advice when faced with management problems. An anti rabies PEP specialized advice clinic is also conducted daily in the Medical Research Institute.

Medical Research Institute was the only rabies diagnostic laboratory in Sri Lanka till December 2002. A decentralized laboratory was established in the southern province in January 2003. Unfortunately this laboratory was completely destroyed by the tsunami which devastated Sri Lanka in December 2004. After going through lot of hardship and effort with the support from the Japanese government, we were able to re-establish the rabies diagnostic lab in the Teaching hospital - Galle in the southern province in August 2006. We hope to start a second lab in the Faculty of Veterinary Science - Peradeniya in the central province by mid 2007. These two labs will strengthen the rabies surveillance programme in the country. Quality assurance and staff training is conducted by the reference laboratory (Medical Research Institute) on a regular basis. Number of suspected brain samples received by the laboratories have increased in 2006 when compared to the previous years and the percentage of laboratory proven rabies samples have decreased over the years.
Rabies week was declared in 2006 by the Ministry of Health, where several training programmes for all categories of staff involved in rabies control activities, mass dog immunization and sterilization campaigns and rabies awareness programmes for the public and school children were conducted with the support from the preventive health staff and the local authorities. New national guidelines on anti rabies PEP was also prepared for better management of patients and also to reduce unnecessary use of rabies immunoglobulins and TCV.

Dedicated staff who cared for the patients, better patient compliance due to fewer adverse events following immunization, commitment and support from the Ministry of Health were the key factors for the success of the ID programme in Sri Lanka. This has been proved safe and effective and at the same time save a considerable amount of foreign exchange for the country.

<table>
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<tr>
<th>Rabies Diagnosis MRI (1999 – 2006)</th>
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<tr>
<td>No. of specimens</td>
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<tr>
<td>Total no. of Positives</td>
</tr>
<tr>
<td>Dogs</td>
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<td>Cats</td>
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<td>Ruminants</td>
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<td>Monkeys</td>
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<td>Mongoose</td>
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<td>Jackals</td>
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<td>Domestic Rats</td>
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<tr>
<td>Humans</td>
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<tr>
<td>Other Animals</td>
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<td>% Positivity of All Animals</td>
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</table>

Table showing rabies incidence in animals and humans as diagnosed in Medical Research Institute, Colombo, Sri Lanka

Incidence of human rabies deaths in Sri Lanka

Hospitals Administering ID Rabies Vaccination 2007

Map of Sri Lanka showing location of hospitals administering ID vaccination
RABIES IN THE PHILIPPINES:
LESSONS LEARNT

Dr. Beatriz P Quiambao
Research Institute for Tropical Medicine
Department of Health, Philippines

The public health burden of rabies arises not only from human rabies cases but also from the thousands of patients potentially exposed to rabies through dog and cat bites.

The goal of the National Rabies Prevention and Control Program (NRPCP) is to declare the Philippines rabies free by 2020. The program strategies include (1) Strengthening of the IEC campaign on anti-rabies program; (2) Organization/revitalization of rabies control Committees at all levels; (3) Strict enforcement of rabies control ordinances; (4) Establishment of functional animal bite treatment centers; (5) Proper implementation of dog vaccination; (6) Ensuring readiness of rural health units in the management of bite patients; (7) Establishment and maintenance of functional regional rabies diagnostic lab and (8) Conduct of disease surveillance.

Over the years, the National Rabies Prevention and Control Program has made a lot of progress towards control of the disease. Notable among the program strategies include (1) rabies prevention program through Curriculum Integration and Instruction which has been implemented in the region with the highest number of human rabies cases with encouraging results; (2) Establishment of functional animal bite treatment centers; (3) Conduct of activities to increase awareness about rabies such as Rabies Awareness Month in March, Swim for a rabies free Philippines, rabies caravan on "responsible pet ownership"; (4) Pre-exposure vaccination of school children and (5) Establishment of regional rabies diagnostic laboratories.

Lessons Learned

1. As rabies is a zoonosis, control of dog rabies remains the most important key to its elimination. Close coordination with the various agencies involved in rabies control is necessary
2. A strong political will and cooperation of the local government units are needed in order to obtain the resources needed for rabies control
3. The role of education cannot be overemphasized
4. There is a need for a quality assurance program to ensure that the ABTCs are managing patients according to accepted guidelines
5. A nationwide surveillance system must be put in place in order to ensure accurate and timely reporting of
6. Since traditional healers still provide medical care in some areas in the Philippines, they may need to be integrated into the program
Graph showing rabies deaths Vs number of animal bites

Mass Education Campaign for rabies prevention and control in Philippines
There are multifaceted issues in Pakistan related to lack of awareness of dog bite and rabies among both patients and doctors, use of obsolete vaccines, insufficient and expensive modern tissue culture vaccines, lack of diagnostic facilities, absence of accurate data, and above all, poor control of stray dogs. At the invitation of “Rabies in Asia” the Pakistan Chapter (RIA Pk) was formed and its first meeting was convened in May 2006 in order to address each of these issues both at federal and at city district levels. Members were inducted from amongst clinicians, veterinarians, epidemiologists, animal rightists, government and non-governmental organizations.

A second meeting was organized in Islamabad June ’06 in the office of the National Institute of Health with the Director General of Health of Pakistan. The objectives of RIA Pk were presented to him and his cooperation was sought. Of serious and immediate concern was the fact that two out of three multinationals had discontinued manufacturing tissue culture vaccines, and the only remaining multinational had raised its price to an unaffordable cost. Consequently, output of nerve tissue vaccine had almost quadrupled. RIA Pk recommended that the Drug Registration Board be advised to allow import of quality vaccine from India which was exporting to most Asian countries.

Subsequently, RIA Pk organized 4 workshops on PEP in Karachi (2) Hyderabad and Lahore. Two more are scheduled for Peshawar and Abbottabad in March, and in Multan and Quetta later in the year. Thus, we will have held Rabies PEP workshops in each province. The workshops were well attended, and interactive. Real patients were brought in and participants were asked to interview them, categorize the wound and advise PEP. Hands-on intradermal application was demonstrated. Participants were given handouts, references and two non-commercial CD documentaries on post exposure prophylaxis.

Although newspapers give out news items about dog bites and rabies from time to time, there are yet no accurate national statistics. RIA Pk has applied for a Wellcome Trust grant for a Pakistan National Rabies Surveillance which would extend to animal and human rabies and dog population control.

RIA Pk office bearers have given numerous radio and television interviews and press statements about its function, drawing prominent newspaper editorials in both regional and English language newspapers.

At the time of submitting this abstract, the Drug Registration Board has licensed at least three local agencies to import quality rabies vaccine from India. This will greatly ease the vaccine shortage in Pakistan and allow for competitive prices. We hope that TCV given intradermally as taught during workshops will allow for more economical and effective PEP.

RIA Pk’s plan of action at this time is to continue public awareness campaigns, teach correct PEP and advocate against Sheep Brain Vaccine. If funds become available RIA Pk will collect national data and set up dog birth control and vaccination camps.
RIA Pakistan members with DG Health at NIH in Islamabad

Rabies Awareness Walk Sept. 2004

Walk for rabies awareness in Karachi, Pakistan
Rabies has been known in China for more than 2,000 years, and was first described ~ 556 B.C. Since 1950, human rabies has been listed as one of the Class-notifiable diseases in China, and thus the annual numbers of human rabies cases and their distribution have been archived. From 1950 to 2005, a total of 110,960 human rabies cases have been recorded in China, with 3 epidemic waves of human rabies in China. In the early 1950s, only a few cases occurred, the first peak occurred in 1956-1957 with ~2,000 cases each year. Then the number of cases declined during the following years and was relatively constant throughout the 1960s. By 1969, the number of cases increased again to ~2,000. This ascending phase continued throughout the 1970s and 1980s. The second epidemic peaked in the beginning of the 1980s. In 1981, 7,037 cases were recorded, the largest number of cases in a single year during the 55-year period. During the 1980s, there were 55,367 reported cases (> 5,000 cases annually), representing >50% of the 108,412 cases seen during the entire period. In the early part of 1990s, the numbers of human cases decreased dramatically from 3,520 in 1990 to 159 in 1996. However, this downward trend reversed its course in 1998 and annual cases have increased gradually since then. In 2005, a total of 2,548 cases were reported. Particularly, the number increased by 30% compared with that in 2005. This shows that the third rabies epidemic is present and its peak is yet reached. Moreover, human rabies suddenly occurred in some areas in 2004, where no human rabies cases had been reported over the ten years, and the incidence rate even reached 10.73 per 100,000 inhabitants. In addition, the percentage of the cases with the incubation period of ~20 days apparently increased in these endemic areas.

Although human rabies cases have been reported in almost all provinces, 15 provinces have had >1,000 accumulative cases each. These provinces are Hunan, Guangdong, Sichuan, Guangxi, Guizhou, Hubei, Jiangxi, Shandong, Henan, Anhui, Jiangsu, Hebei, Fujian, Yunnan, and Liaoning. These 15 provinces account for >93% of the total cases. Four provinces (Hunan, Guangdong, Sichuan, and Guangxi) have had >7,000 accumulative cases each.

To better understand the current rabies epidemics in China, we isolated rabies viruses from dogs and humans from five provinces (the major endemic areas) and characterized these isolates genetically by sequencing the entire nucleoprotein (N) gene. Comparison of the N genes among these isolates revealed 86.6-99.9% homology and these viruses could be located the two phylogenetic clusters with 4 lineages. Interestingly, the Chinese viruses of one phylogenetic group have a close relationship with viruses circulating in Asian canine population, particularly with the viruses derived from Indonesia.

The rabies epidemics in China since 1950 may be partially explained by dog population dynamics. The first major epidemic subsided at the end of the 1950s and the beginning of the 1960s, coinciding with pet reduction policy. The second major epidemic peaked in the late 1970s and early 1980s, when the economic reform was initiated in China and dog population increased dramatically. Population immunity may also play a role in these cyclic epidemics. However, the dramatic decline of rabies cases in the early part of 1990s or the initiation of the third epidemic around the turn of the millennium could not be explained simply by dog population dynamics. Other factors may include untimely and inappropriate post-exposure treatment for human and the low inoculation coverage for dogs.
In summary, rabies remains a public health problem in China. Strategies to control and prevent human rabies include public education and awareness about rabies, pet vaccination programs, elimination of stray animals, and enhancing post-exposure management.

Graph depicting rabies incidence in China from 1950-2005
Rabies is an almost invariably fatal, acute viral encephalomyelitis. Infectious Agent of rabies virus is a rhabdovirus of the genus Lyssavirus. It is prevalent worldwide, with an estimated 35,000-40,000 deaths a year. Its reservoir are many wild and domestic Canidae, including dogs, foxes, coyotes, wolves and jackals; also skunks, raccoons, mongooses and other biting mammals. The disease occurs in both sylvatic and urban foci. Foxes and jackals probably are the most important sylvatic reservoirs whereas dog is the most important domestic species for rabies transmission. In contrast, dogs are the principal vectors for transmission of rabies to human and domestic animals in countries like Nepal where there are a large proportion of stray dogs.

Rabies is endemic in Nepal. Several rabies outbreaks have been reported throughout the year from various parts of Nepal. Hundreds of human cases seek post-exposure treatment against rabies every year and more than 100-150 people die of hydrophobia annually. In countries belonging to the South Asia Association for Regional Cooperation (SAARC), rabies is considered to be a priority infectious disease. Animal rabies outbreaks have been recorded from different parts of the country. There were 39 outbreaks reported in 75 districts of which 1470 animals were affected of which 270 due to rabies and 361 treated with post exposure treatment and 3488 dogs were immunized in 1999/2000. About 94% of rabies cases in human are caused by the bites from rabid dog, occasionally the cats and other animals. In Nepal about 100-150 persons die due to rabies and nearly 30,000 people take post exposure treatment every year.

The total dog population in the country is estimated at about 1849110. Dog population control in Nepal is attempted primarily through strychnine poisoning campaigns run by local municipalities to eliminate stray or unconfined dogs. Dog poisoning approach is culturally inappropriate for religious and other reasons in some countries, such as Nepal. National Zoonoses and Food Hygiene Research Centre has started free dog and cat rabies vaccination programme with the support of Donative Unit for Rabies Vaccine to Nepal (DURVC) Tokyo, Japan from 2000 till to date in Kathmandu Valley and outside Valley. So far 17 municipalities has been completed dog and cat rabies vaccination campaign. So far NZFHRC has completed dog rabies vaccination programme in 16 municipalities of Nepal.

During the first and second phase of free dog rabies vaccination the 25000 dogs have been vaccinated in Kathmandu valley only and about 15,000 dogs and cats vaccinated in out of outside Kathmandu valley. The future plan of our center is to cover all 58 municipalities of the country. It has been evaluated four baits, using a two-choice bait preference test, in owned dogs in rural Nepal. Chicken head baits were either completely or partially consumed by 42 of the 50 dogs or 84% of the time, which his proved to be best bait for oral immunization in dogs of Nepal. Dog rabies vaccination and future rabies control plan was prepared and published by NZFHRC. Introduction of tissue culture technology in rabies vaccine production, legislation on compulsory immunization of dogs against Rabies; birth control of stray dogs, establishment of a good rabies diagnostic laboratory facility, mass vaccination of dog population once a year with tissue culture Rabies vaccine, sterilization of dogs instead of poisoning dogs and animal care services for all animals and birds to be provided are the main strategies of this plan to be implemented.
Map of Nepal showing distribution of rabies cases district wise

Map of Nepal showing coverage of dog vaccination
Rabies is a disease of Public Health importance that claims 55,000 lives globally. The disease affects people from the lower socio economic strata and is mostly neglected by the health planners and national authorities. The burden of the disease is most felt in developing countries and the impact is felt both on the medical and veterinary fronts. The lack of resources serves to compound the problem in these countries. The shift of priorities to other new and emerging diseases has only added to the neglect of rabies.

It is evident that there is a need for coordination and convergence of activities at all levels. At the global level coordination is in place with the WHO, OIE and other regional forums like RITA, SEARB, RIA and other organizations.

In a country like India with 17.4 million exposures and 20,000 deaths there is no national programme for rabies prevention. Though there are many organizations working for the control of the disease, there is no coordination or networking amongst these organizations which mostly work in isolation.

The presentation will focus on the current problems and the way forward at the global, national and local levels. The presentation will highlight the roles of different stake holders at these levels and will also focus on the successful ventures in the context of India (APCRI) as a model for rabies prevention activities.
Rabies is one of the oldest diseases known to mankind and is prevalent in India for thousands of years. Mention of this disease is made in Hindu Scriptures and probably the word rabies is derived from Sanskrit word "Rabhas" meaning "to do violence". Scientific study of the disease and its prevention started as early as 1895, soon after the landmark discovery of first ever rabies vaccine by Louis Pasteur in 1885. Pasteur Institutes of Northern and Southern India were established during that time at Kasauli and Coonoor respectively to manufacture crude nerve tissue derived vaccines for the treatment of animal bite victims. Another landmark development took place in 1911 when Sir David Semple produced the sheep brain vaccine at the Central Research Institute, Kasauli. This vaccine popularly known as Semple vaccine was used for many decades till the modern cell culture vaccines were made available in early eighties. The pioneer institutes in India to carry out need based research and development work in post independent India were the Central Research Institute, Kasauli (Himachal Pradesh, North India) and Pasteur Institute of India (Coonoor, South India). It was here that carrier state in dogs was reported for the first time with scientific evidence. This report which raised a lot of controversy will nevertheless remain in the history of rabies for ever. These institutes produced not only the vaccine but also produced a good quality rabies conjugate necessary for diagnosis of rabies in animals and humans. They offered training and also provided seed virus and other requirements to 12 other rabies vaccine manufacturing units started in individual states. Other institutes where impetus for rabies research was given include Haffkine’s Institute in Mumbai, IVRI, Izatnagar, UP and National Institute of Communicable Diseases (NICD) Delhi and Madras Veterinary College, Chennai. Presently rabies research has been diverted to many other centers across India. Notable among these include Department of Neurovirology, NIMHANS, Bangalore which is a WHO collaborating center on reference and research on rabies, Indian Institute of Science (IISc), Bangalore, University of Agricultural Sciences (UAS), Bangalore, Kempegowda Institute of Medical Sciences (KIMS), Bangalore and some laboratories in the private sectors. The research in these institutes has been mainly need based and concentrating on development of newer vaccines and newer economical intradermal schedules for post-exposure prophylaxis. An effective DNA vaccine has been developed at the IISc which is now approved for use in dogs. The UAS in collaboration with NIMHANS is working on development of plant based rabies vaccines. Some basic and applied research is being conducted at NIMHANS particularly in the pathogenesis of rabies and development of newer diagnostic tests for ante mortem diagnosis of human rabies. Contrary to expectations, it was found that apoptosis may not have a significant role in the pathogenesis of naturally occurring rabies in dogs and humans. For the first time in India, murine monoclonal antibodies to rabies N and G proteins have been developed which have great therapeutic and diagnostic potential. For the first time it was shown that presence of immune complexes to rabies G and N protein in the CSF of patients may serve as a diagnostic marker of human rabies. RT-PCR and Real time PCR have been standardized for diagnosis of rabies. Extensive work is being carried out in the molecular epidemiology of rabies and many street viruses from different prts of India have been characterized and their sequences have been deposited in the Gene Bank. Full length sequencing of rabies genome is now under progress. Both rabies G and N protein genes have been cloned in baculovirus vectors with high level of expression.
The rabies research in India is not just confined to laboratory. The Department of Community Medicine, KIMS, Bangalore carried out a multi-centric epidemiological survey to assess the burden of human and animal rabies in India. This survey was financed by the WHO. This survey revealed that in India still about 20,000 people die of rabies and an astounding 17 million people are bitten by dogs and other animals every year.

The private sectors have been contributing to a great extent in prevention and control of rabies. It is a matter of pride that cell culture rabies vaccines produced in India are now exported for use in many Asian countries. High quality rabies immune globulins are also manufactured and exported. Oral rabies vaccines for use in dogs have been developed which are likely to be licensed soon. This is likely to boost up the canine rabies control.

List of institutes engaged in rabies work in India

- NIMHANS, Bangalore, a WHO CC
- NICD, Delhi, a WHO CC
- Pasteur Institute, Coonoor
- CRI, Kasauli
- Indian Immunologicals, Hyderabad
- Indian Institute of Science, Bangalore
- University of Agricultural Sciences, Bangalore
- Veterinary College, Chennai
- IVRI, Izatnagar
- Kempegowda Institute of Medical Sciences (KIMS), Bangalore
- Intervet, Pune
- Serum Institute of India, Pune
- Bharat Biotech Hyderabad
- Chiron vaccines, Ankleshwar
- Zydus Alidac, Ahmedabad
- Bharat Serums & Vaccines
A Rapid Diagnostic test developed at NIMHANS, Bangalore

Another test developed at NIMHANS, Bangalore
Results

Gel picture of Nested RT-PCR on Human Saliva samples

RT-PCR for ante-mortem diagnosis of human rabies
Human rabies cases in the Kingdom were reduced from over 400 annually 3 decades ago to less than 20 in 2006. This was largely done by providing public education, replacing Semple and SMB vaccines by effective tissue culture products and making post exposure vaccination available throughout the country for free or at an affordable cost. Nevertheless, three human cases that did not receive vaccination occurred during the month of January 07 in Bangkok. This only reminded us that the disease is still out there among the vector dogs. It is only when it is controlled there, that we can relax. Several recent studies from Bangkok have again shown that rabies vaccine induces decade lasting immune memory whether administered as a pre- or post exposure series. This has implications for potential pre-exposure immunization of children that are at high risk. Vector control, using humane canine population reduction methods and universal dog vaccination, are the main focus of our current efforts. Several Thai government-funded studies dealing with the sequencing of lyssaviruses, their presence in bats and pathogenesis of rabies are ongoing. Chulalonkorn University Hospital staff made an attempt to reproduce the human rabies survival schedule used at Wisconsin in 2005 where a 16-year old girl survived from rabies. We could not claim success. There is new interest in a topic that has been largely neglected or avoided at rabies conferences: the fact that even apparently perfect post exposure treatment of exposed persons is not 100 percent effective. Several well-documented treatment failure cases from Thailand and elsewhere have been identified and will be discussed.
Human rabies is almost always fatal. Ketamine was one of the therapeutic agents used on a rabies survivor in Wisconsin who did not receive vaccine. The therapy was based on previous experimental work performed in primary neuron cultures and in a rat model of rabies. We have reexamined ketamine therapy in infected mouse primary neuron cultures and in adult ICR mice using the CVS strain with both intracerebral and peripheral routes of inoculation with ketamine (120 mg/kg/day) vs. vehicle given intraperitoneally. We did not observe any significant beneficial therapeutic effect of ketamine in the cultures or mouse models. We do not recommend further widespread clinical use of ketamine on human rabies patients until further experimental work confirms therapeutic efficacy.

Because of the potential neuroprotective and anti-apoptotic properties of minocycline, we also assessed minocycline therapy in infected primary neuron cultures and in neonatal ICR mice infected by peripheral inoculation with a highly attenuated rabies virus strain (D29). No beneficial effect of minocycline was observed in the primary neuron cultures. In the mouse model, minocycline therapy (50 mg/kg/day for 18 days) aggravated the clinical neurological disease and resulted in higher mortality. An anti-apoptotic effect of minocycline was noted in brains of infected mice, which may have very mildly increased viral spread. An anti-inflammatory effect of minocycline was also noted in the brain using a CD3 T cell marker. These effects likely aggravated the disease. Consequently, we recommend that empirical therapy with minocycline be avoided in the management of rabies and viral encephalitis in humans until the results of more experimental work becomes available.

The therapeutic approach to human patients with rabies will be discussed, including the use of therapeutic (induced) coma.
Rabies is still present in Europe in 2007. Its incidence in humans remains limited (fewer than 5 human cases per year) through the application of strict prophylactic measures (anti-rabies treatment) and by means of veterinary rabies control measures in the domesticated and wild animal populations. Three lyssavirus genotypes are endemic: genotype 1 or rabies virus (RABV), which infects terrestrial animals, and genotypes 5 and 6 or European bat lyssavirus type 1 (EBLV-1) and type 2 (EBLV-2). The main indigenous animal reservoirs are: the dog in eastern European countries and on the borders with the Middle East; the fox in central and eastern Europe; the raccoon dog in northeastern Europe; and the insectivorous bat throughout the entire territory. The decline of vulpine and canine rabies highlights the emerging risks related to the increase in travel to regions where rabies is enzootic and the increase in contacts between humans and bats.

Each year, cases of animals with rabies imported from enzootic areas are reported, showing the permeability of borders and traveller's lack of consideration of the rabies risk. These importations constantly threaten the rabies-free status of terrestrial animals in western European countries and complicate the therapeutic decisions taken by physicians in the absence of information regarding the biting animal. This risk is increased by the freedom to travel within the European Union, and it is therefore mandatory for these countries to educate their populations regarding anti-rabies measures so that they can react rapidly to an importation incident. Collaborative research studies between regions at risks and Europe would then be beneficial for each part. These would help enzootic regions to control and potentially eliminate rabies and in the same way considerably limit the risk of re-introduction of rabies in Europe and the risk for European travelers. An example of these is given by the recently started EU funded program, RABMEDCONTROL.

EBLV-1 and EBLV-2 circulate among several bat species and numerous bats are found infected each year. These viruses can also cause a fatal illness, indistinguishable from classic rabies, in non-flying mammal species, including humans. Therefore, bat rabies is a public health concern in Europe. However, the epidemiology and the pathogenicity of EBLV in bats are still unknown. In particular, little data are available on the spatio-temporal dynamics of the infection and how this virus influences the mortality rate in bat colonies. Studies addressing these issues require large databases, collected over years, to monitor and assess local trends of rabies dynamics within a host population. The collection of such data has now started in Europe.

Lyssaviruses have established sustained transmission networks in a variety of terrestrial carnivores (dogs, jackals, foxes, raccoons, mongoose, skunks) as well as many different bat species (hematophagous, insectivorous and frugivorous) in the world. All lyssaviruses are adapted closely to their preferred host, which serves as a vector for transmission. However, they have kept the capacity of infecting all other mammals, albeit with a much lower probability of success compared to their preferred host. In case this infection is successful, these other mammals act as secondary host species in the epidemiological cycle and constitute often dead end infections. The susceptibility of humans to these related viruses is highly variable, dog viruses causing more than 95% of the human deaths. As for the other RNA viruses, the basic molecular mechanisms involved in this process of adaptation are poorly understood although this information is crucial to the greater goal of controlling lyssavirus infection in the field and preserving human health. The identification of the evolutionary events that, from the viral side, are involved in host specificity would then help us to understand the mechanisms involved in the crossing of species barrier and in the changing of hosts.
Graph showing incidence of animal rabies in Europe

Map of Europe showing prevalence of dog rabies
Newly discovered Lyssaviruses in Europe and Asia

Graph showing incidence of bat rabies in Europe
In spite of the lack of major support from international funding agencies, rabies research has made remarkable progress in the past decade. This progress has been made as a result of collaboration efforts between researchers in the East and West. For example, data provided from clinical trials initially conducted in Europe and North America and later in Asia have provided the WHO with enough proof that lower dose intradermal regimens are efficacious for post-exposure prophylaxis (PEP). This has enabled countries with limited budgets for health care to replace outdated and dangerous nerve tissue rabies vaccine with the much safer cell culture rabies vaccines. Transfer of modern cell culture vaccine technology to developing countries has also reduced the production costs of cell culture rabies vaccines in regions where canine rabies continues to cause millions of human exposures to potentially rabid animals every year. With the increased availability of cell culture rabies vaccines in highly endemic regions, the focus has begun to shift toward improving the availability of another life-saving rabies biological; ie rabies immune globulin. The ever expanding field of monoclonal antibody (Mab) technology initially developed in the West has revolutionized therapeutic treatments for many diseases and conditions throughout the world. The opportunities for the development of Mabs for administration as part of PEP regimens are plentiful. Several recent publications have proven that various Mabs when used in combination with rabies cell culture vaccine are efficacious. Collaborative efforts to transfer this technology from the West to the East, where canine rabies continues to pose a major threat to human health, are underway. This effort needs to be afforded the greatest encouragement possible. One only needs to investigate the progress made in the field of Mabs developed for the treatment of other diseases organisms to realize the fact that Mabs hold the best promise for improving the current rabies PEP. For example, Mabs can significantly lower the cost of passive treatment for PEP while simultaneously providing equal or even improved efficacy as well as the technology to dramatically increase the production capacity and thereby extend the availability of this life-saving biological to populations that need it most. As rabies advocates, we all should give serious consideration to endorsing the development production facilities that will provide access to this new technology.
Rabies is enzootic in India. It exists as urban form with domestic dogs as the principal reservoir. Other domestic and wild animals also transmit the disease to human beings. The disease occurs throughout the year in all parts of the country except Andaman and Nicobar Islands. Urban dog rabies presents the greatest risk both to human and animal health. Persistence of rabies virus in the stray dog population poses a real challenge to achieve a meaningful reduction of either incidence or burden. Attempts are being made to control rabies through mass vaccination practices and Animal Birth Control Programs with support from both the State governments and Animal Welfare Board of India. Approximately, 70,000 dogs are covered under this program annually. The epidemiology of rabies in India and various control measures adopted will be discussed.
Dog vaccination and control of stray dogs as rabies control measures launched in Sri Lanka since 1975 have had a significant effect on the incidence of human rabies. The number of human rabies deaths declined from 377 in 1973 to 68 in 2006.

The dog is the main reservoir as well as the transmitter of rabies in Sri Lanka. Over 90 per cent of animal rabies was reported among dogs. In addition rabies had been confirmed in cats, cattle, goats, Pole cats, Bandicoot, and Mongoose too. A dog ecology study conducted in 1980s has revealed a dog to human population of 1:8. A dog ecology study conducted during 1997, in Mirigama, a recently urbanized area reveals dog population ratio of 1:4.6. Further, the study indicates that 20 per cent of the dogs were ownerless. Recent studies conducted in districts have revealed that the ratio is 1:20 in some peripheral district. Rapid urbanization has led to an increase of the dog population.

**Table (i) Progress of dog rabies control and Human rabies situation**

<table>
<thead>
<tr>
<th>Year</th>
<th>Vaccination</th>
<th>Elimination</th>
<th>Human Deaths</th>
<th>Deaths</th>
<th>Rate/100,000</th>
</tr>
</thead>
<tbody>
<tr>
<td>1970</td>
<td>11844</td>
<td>688</td>
<td>262</td>
<td>2.1</td>
<td></td>
</tr>
<tr>
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<td>42252</td>
<td>1610</td>
<td>288</td>
<td>2.1</td>
<td></td>
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<tr>
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<td>268561</td>
<td>58238</td>
<td>113</td>
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<td></td>
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<tr>
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<td>412586</td>
<td>63233</td>
<td>154</td>
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<td></td>
</tr>
<tr>
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<td>657597</td>
<td>117790</td>
<td>109</td>
<td>0.6</td>
<td></td>
</tr>
<tr>
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<td>818161</td>
<td>63515</td>
<td>55</td>
<td>0.4</td>
<td></td>
</tr>
<tr>
<td>2006</td>
<td>956637</td>
<td>11081</td>
<td>68</td>
<td>0.4</td>
<td></td>
</tr>
</tbody>
</table>

**Current Development in Dog Rabies Control**

In the year 2005 non-governmental Animal welfare organizations protested against stray dog elimination. As a result Government took a decision to avoid indiscriminate killing of dogs. Dog elimination was gradually reduced and Stray dog vaccination was introduced as an alternative. Over 50,000 stray dogs were vaccinated using auto-vaccinators in 2005 and 70000 stray dogs were vaccinated in 2006. Further Animal birth control was introduced as a new strategy to reduced stray population. Nearly 50,000 stray females were injected with medroxyprogesterone acetate (MPA) and 1500 owned dogs were subjected to surgical sterilization.
Dog Rabies Elimination plan

In 2005 Government decided to eliminate rabies by 2016. As a result a ten year plan has been prepared for required capacity building to achieve the government goal.

Table (ii) Progress and Future projection for control of Dog rabies and strays

<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td></td>
<td>637000</td>
<td>644000</td>
<td>956637</td>
<td>1300000</td>
<td>1800000</td>
</tr>
<tr>
<td>Surgical Sterilization</td>
<td>0</td>
<td>0</td>
<td>1500</td>
<td>10000</td>
<td>50000</td>
</tr>
<tr>
<td>Dogs injected with MPA</td>
<td>0</td>
<td>0</td>
<td>40502</td>
<td>100000</td>
<td>200000</td>
</tr>
</tbody>
</table>

Mission: Development of infrastructure facilities, Human resources and other logistic support for achievement of objectives

Table (iii) Progress and Future projection for Human rabies incidence

<table>
<thead>
<tr>
<th></th>
<th></th>
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<td></td>
<td>109</td>
<td>76</td>
<td>68</td>
<td>35</td>
<td>10</td>
</tr>
</tbody>
</table>

Strategies to Reach the Goal of Rabies Elimination

1) Capacity Building for mass immunization of dog.
2) Capacity Building for Promotion of humane methods of controlling 'stray' dog rabies.
3) Increasing awareness on rabies and responsible dog ownership among public.
4) Capacity Building for island wide rabies surveillance by establishing a network of rabies diagnostic labs.
5) Establishment of collaborative partnership with Livestock, Local government and NGO sectors.
6) Development policies and legislations to ensure effective implementation of above strategies.

Constraint

Existing political situation in the country and lack of donor support.

Opportunities

Rabies Elimination has been included in government highest priority program "Mahinda Chinthana" and closely monitored by his excellencies President's office.

Conclusion

Sri Lanka being an island having a well-established network of health services which had already coordinated several disease elimination programs is very favorable to launch rabies elimination.
Graph showing decline of rabies deaths as vaccination coverage increased

Graph showing number of dog vaccination over the years
Vaccination of street dogs with auto-vaccinator in Sri Lanka
Rabies remains one of the most dreadful infectious diseases affecting human and animals despite significant scientific advances in prevention and control. Rabies presents as a distinct problem in different parts of the world. In the more industrialized nations, the risk to human beings has minimized significantly, mainly due to mandatory vaccination programs of dogs and other pet animals. Although wildlife rabies still exists in the developed countries, most impressive progress has been made in control and elimination of wildlife rabies using oral immunization of wild carnivores. In contrast, rabies remains a major threat to public health and persists to cause numerous human deaths in the less industrialized nations.

Rabies is still epizootic in most countries of Africa, Asia and South America and in these countries dogs are responsible for most human deaths from the disease. Dog rabies control relies principally on the mass immunization of dogs in order to achieve population immunity levels sufficient to inhibit rabies transmission. This approach was very successful in countries like Mexico and Brazil. However, the presence of large numbers of "ownerless" dogs that are not accessible for parenteral immunization contributes greatly to failure of vaccination programs in African and Asian countries. Large scale vaccination program was very successful in Latin America. Introducing new control strategies in addition to the existing parenteral vaccination programs is a necessity.

Live oral Rabies vaccines have already been used for decades in Europe and USA to control wildlife rabies. Wildlife rabies control was initiated for the first time by introducing oral rabies vaccination in 1978 and its field application was first time introduced in Swiss Rhone Valley. Later on oral rabies vaccines were used in other parts of Europe and USA. Oral Vaccine dosing in developed countries was done by spreading baits east to west and then vice-versa during first vaccination. Second vaccination was carried at 2-4 weeks later after first vaccination by spreading baits north to south and back by plane. Thus effective implementation of two bait vaccinations on annual basis in wildlife has enabled developed countries to bring down rabies incidences to a minimum level. Live oral rabies vaccines used in wildlife for foxes in Europe and Raccoons in USA were considered not safe enough by WHO and Indian authorities. SAD B19 is still widely used in Europe whereas in France in addition SAG-2 has been mainly used. However, in USA only the vaccinia recombinant vaccine VR-G is licensed and widely used.

Most of the rabies deaths in humans are due to dog bites in particular stray- or community-owned dogs. An effective and economical tool to combat this threat would be oral immunization of these dogs by a bait delivery system in addition to parenteral vaccination of reachable pets. However, the attenuated live rabies vaccine strains used worldwide are considered not safe enough by the Indian authorities. Hence, we have initiated the improvement in the safety and efficacy of the wildlife rabies vaccine to allow its use to control canine rabies in stray and ownerless dogs.

Our recent development by stepwise further attenuation using reverse genetics leads to improved safety of the original SAD strain. First a SAD mutant has been derived wherein the Arginine residue of Glycoprotein G at position 333 is stably replaced with Aspartic acid (to obtain strain ORA-D). ORA-D is non-pathogenic for adult mice given intracerebrally (IC), but possesses some residual pathogenicity for baby mice if given IC. Then a further small deletion of 7 amino acids was introduced into the P-protein. This removes the putative LC8 binding site, thereby preventing axonal transport of the virion core along a neural tract. These
steps lead to the development of a stable ORA-DP vaccine virus, which is now even safe in 1-2 days-old suckling mice after intramuscular inoculation. To enhance the immunogenicity, the ORA-DPC strain has been developed by inserting an additional glycoprotein G derived from the CVS-strain (which included the replacement of Arg to Asp at 333). The insertion even further improves the safety profile of the strain. This modified ORA-DPC vaccine strain has shown extreme degree of attenuation even in immunosuppressed dogs as well as nude and SCID mice. There are no rabies related clinical signs or virus excretion in immunosuppressed dogs even after vaccination with higher dosage. Its enhanced immunogenicity induces increased neutralizing antibody titers even in immuno-suppressed dogs. Irrespective of antibody titres, the vaccinated animals do resist rabies virus challenge. ORA-DPC is the efficacious and the safest candidate, live attenuated rabies vaccine strain available for oral immunization of dogs.

The oral vaccine strains developed through ‘reverse genetics’ technologies are genetically stable and very safe, even in immuno-compromised animals. In addition, they are efficacious in protecting the vaccinated dogs after oral immunization. The most promising strain being ORA-DPC, hence providing an effective tool for oral vaccination of stray and community-owned dogs, and with a suitable bait delivery system, it is an excellent option.

WHO expert consultation committee meet on Rabies has identified mass immunization as the single most effective tool for dog rabies control whereas dog culling alone is ineffective one. In addition, this international body has also recommended the oral vaccination as a complementary method in dogs, in addition to IM and SC routes of vaccination. In such situation, ORA-DPC can play a great role to control canine rabies in Asia and Africa.

The triple mutant ORA-D is genetically stable in suckling mice passages and in more than 25 cell culture passages in the absence of any Mab.

Genomic organization of genetically engineered rabies virus
Efficacy of Extensively Attenuated Oral Rabies Vaccine Candidates in Dogs

Graph showing efficacy of attenuated rabies virus candidates
The annual number of worldwide rabies deaths in humans is estimated at 40,000-70,000, and 30-50% of rabies deaths are among children under the age of 15 years. Though invariably fatal, rabies is vaccine preventable. The recommended effective rabies post-exposure treatment uses inactivated tissue culture rabies vaccine plus rabies immunoglobulin (RIG) injected into and around the bite wound(s). Rabies immunoglobulin is expensive and often in short supply or not available when and where needed most. Thus, many human rabies victims do not receive effective post-exposure treatment, or it is rendered late or incomplete.

Pre-exposure rabies prophylaxis (PEP) can protect persons with unrecognized exposure to rabies and allows persons who may later be exposed to rabies virus to be protected by only 1-2 post-exposure doses of rabies vaccine without RIG. PEP is also an important approach in children, since exposure to animals is not always identified. A three-dose intramuscular (IM) or intradermal (ID) PEP using tissue-culture rabies vaccine is recommended by the World Health Organization (WHO).

We conducted a PEP study in Thailand among 190 school children aged 5-12 years using PVRV (potency 4.64 IU/0.5 ml) IM or ID on days 0, 7, 28 and a booster dose at one year. On day 56, the IM and ID group had achieved WHO acceptable protective antibody titers (>0.5 IU/ml) of 100% and 99%, respectively. Seven days after 1-year booster, all children had antibody titers above the protective level.

Two hundred Vietnamese infants received PVRV PEP (potency 3.5, 6.4, and 12 IU/0.5 ml) ID at 2, 3, and 4 months of age at the same time as EPI vaccines-diphtheria, tetanus, whole-cell pertussis, and inactivated poliomyelitis combined vaccine (DTPw-IPV)-compared with PVRV IM at 2 and 4 months of age. One month after the last dose of vaccination, all the ID group (GMT 12 IU/ml) and IM group (GMT 30.6 IU/ml) had acceptable protective antibody titers. Adverse events were mild and transient. There was no evidence of interference between DTPw-IPV and rabies vaccine.

Two hundred Thai children aged 12-18 months received PCEC (potency 7.25 IU/ml) PEP ID or IM at the same time as inactivated Japanese encephalitis vaccine (JEV) in EPI on days 0, 7, 28 and 1-year booster. On day 49, all children had antibody titers above protective level. Seven days after the booster, all children also had antibody titers above the protective level. The antibody titers of IM route were 2-fold higher than the ID route. Adverse events were mild and transient. There was no interference between JEV and rabies vaccine.

In conclusion, inactivated tissue culture rabies vaccine can be administered as PEP at the same time with DTPw-IPV and JE vaccination without antibody interference. While IM route give superior immunogenicity results in PEP, the ID route can also be used.
Graph showing neutralizing antibody response to pre-exposure vaccination and booster dose
COMPARATIVE STUDY ON IMMUNOGENICITY, SAFETY AND TOLERANCE OF PURIFIED DUCK EMBRYO VACCINE (PDEV) MANUFACTURED IN INDIA (VAXIRAB) AND SWITZERLAND (LYSSAVAC)

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2. Department of Neurovirology, National Institute of Mental Health and Neurosciences (NIMHANS), Bangalore, India
3. Institute of Preventive Medicine, Hyderabad, India
4. Pasteur Institute, Kolkata, India
5. Cadila Healthcare ltd, Ahmedabad India.

Rabies and rabies prophylaxis is a major health concern in Asian Countries. In India alone 20,000 people die of rabies and nearly 8 million people undergo post exposure prophylaxis due to animal bites. Consequent to the stoppage of the production and use of Semple vaccine there is a huge demand for modern rabies vaccines. In this context the introduction of a purified duck embryo vaccine (PDEV) manufactured in India with technology transfer from Berna Biotech, Switzerland is a welcome step. This study was done to assess the safety, immunogenicity and tolerance of PDEV manufactured in India (VaxiRab) in comparison to that manufactured at Switzerland (Lyssavac). Healthy volunteers from three centers (Bangalore, Hyderabad and Kolkata) were recruited for the study. One hundred and twelve persons were administered VaxiRab and 109 were administered Lyssavac by intramuscular route using Essen regimen. The subjects were followed for 6 months and adverse reactions were recorded. Antibody titers were estimated by rapid fluorescent focus inhibition test (RFFIT) on days 0 (before vaccination) 14, 30, 90 and 180 post vaccination. None of the subjects had neutralizing antibody titers on day 0. All subjects in both the groups developed adequate titers by day 14. Both the groups had more than adequate titers on day 180. The Geometric mean titers on different days for VaxiRab was 10.3, 14.3, 7.3 and 3.7 IU/ml and for Lyssavac was 10.9, 15.1, 10.2 and 5.3 IU/ml respectively. There was no significant difference between the titers on days 14 and 30 but the titers with Lyssavac were significantly higher on days 90 and 180 (P <0.0001). The total adverse reactions to VaxiRab were 13% that was significantly lower when compared to Lyssavac that was 18.5% (P<0.02). To conclude, this study has shown that PDEV (VaxiRab) manufactured in India is highly immunogenic, safe, well tolerated and comparable to PDEV (Lyssavac) manufactured at Switzerland. This vaccine along with other modern vaccines will go a long way in meeting the ever-increasing demand for safe and effective rabies vaccines in India and other Asian countries.
Neutralizing antibody titres obtained with Vaxirab and Lyssavac on different days
Persons having a confirmed or suspected Rabies exposure for the first time are assured of getting a standard and scientifically correct treatment with 5 doses of Tissue Culture Vaccine against Rabies[TCV] and where indicated an appropriate dose of Rabies Immunoglobulin[RIG] of either equine or human origin. This will also hold good for all those persons seeking medical treatment for the first time even in a case of repeat exposure where no treatment was taken for the previous exposure(s). There is unanimity in this in all parts of the world.

In the case of persons who had received a complete course of vaccination with 5 doses of TCV and where indicated, RIG, appropriately, for a previous exposure, there are different practices in different countries.

WHO guidelines mention about a standard 2 booster doses protocol, of a booster each on Day0 and on Day3, in re-exposure cases, whatever time interval has elapsed since the first complete course of TCV.

WHO guidelines, also mention about newer vaccines, to provide clinical evidence, that they are immunogenic and safe, before they can be used in any schedule of vaccination. Clinical evidence should include clinical trials involving the use of serological testing with RFFIT, and publication in internationally peer-reviewed journals.

Not all, TCVs in use in different countries have generated this kind of data in re-exposure cases, and more so in long duration re-exposure cases.

Scientific studies published in internationally peer-reviewed journals of repute, mention some very interesting facts in long term re-exposure studies and pre-exposure studies. These studies were done with HDCV and PVRV manufactured by Sanofi Pasteur only. However the package insert of both HDCV and PVRV manufactured by Sanofi Pasteur [the vaccines used in those clinical trials], mention about a full course of vaccination in cases seeking treatment for re-exposure after five years of the first complete course of vaccination with WHO approved TCVs. This has been done as the manufacturers feel that there is not enough data to make any modification without putting the recipient [the patient] at risk, considering the almost 100% fatality of Rabies.

The package inserts of vaccines not having supporting data to prove that they are immunogenic and safe when used in re-exposure or long term re-exposure cases, are mentioning about only 2 boosters, one each on Day0 and on Day3, in re-exposure cases, whatever time interval has elapsed after the primary complete course of PET with 5 doses of TCV. Many prospective follow up studies on patients receiving full course PET, and boosters given after many years is needed, here.

These are the realities of the information available in the management of re-exposure cases. I sincerely hope that some day a uniform standard protocol will emerge in the treatment of re-exposure cases after proper scrutiny of all the information available and help clinicians like me to provide ethical, safe and scientific treatment to the animal bite victims. At least 15% of all cases attending an anti-rabies treatment center are re-exposure cases.
Rabies is an acute viral disease that is considered to be fatal once clinical symptoms develop. With an estimated 55,000 deaths per year worldwide, human rabies remains a major health problem. In Asia, more than 30,000 human rabies deaths are estimated to occur each year. The highest death rate occurs in children with 45 to 60% of human victims being less than 15 years old.

Today, vaccination is considered the only means to prevent the disease in humans; either as pre-exposure prophylaxis or after exposure to rabid animals in combination with wound management and administration of anti-rabies immune globulin. While travelers from Europe and the US to rabies endemic countries are often protected by pre-exposure vaccination, in Asia, post-exposure prophylaxis has been the predominant approach to rabies prophylaxis. As children are particularly vulnerable to dog bites, the WHO currently recommends pre-exposure prophylaxis as a means to protect children living in or visiting high risk areas where there are no canine vaccination and control programs in place.

This presentation summarizes the clinical data obtained in several clinical trials throughout Asia after vaccination of children with Purified Chick Embryo Cell rabies Vaccine (PCECV). Clinical trials have been performed in age groups from toddlers to schoolchildren, using intradermal (ID) as well as intramuscular (IM) vaccination schedules.

Pre-exposure studies were conducted at four centers, viz., Mumbai, India (I49P5) where 150 children were recruited; Bangkok, Thailand (M49P2) where combined rabies and JE vaccination was studied; in Phetchabun province of Thailand (I49P1) where 703 school children were included and in Philippines (I49P7) where 150 subjects were included.

In all clinical studies, the vaccine was well tolerated.

Immunogenicity results demonstrate that pre-exposure prophylaxis with PCECV in WHO recommended 3-dose regimens (IM or ID) provides virus neutralizing antibody titers, which are considered protective against rabies.
Recently a pre-exposure study was undertaken at Mumbai, India

Graph showing antibody response to pre-exposure vaccination
Pre-exposure study undertaken at Bangkok, Thailand

Graph showing antibody response to pre-exposure vaccination at Bangkok, Thailand
Pre-exposure study undertaken at Phetchabun, Thailand

Graph showing antibody response to pre-exposure vaccination at Phetchabun, Thailand
Pre-exposure study undertaken in Philippines

Graph showing antibody response to pre-exposure vaccination in Philippines
Passive immunization is an important parameter of post exposure rabies prophylaxis. Two types of rabies immunoglobulin (RIG) are currently available for Passive immunization against rabies i.e., human rabies immunoglobulin (HRIG) and equine rabies immunoglobulin (ERIG). The former is very expensive and not easily available and the latter causes side effects because of which its utility is limited. In the present study we have produced murine monoclonal antibodies (Mabs) to rabies glycoprotein (G) and studied their utility in passive immunization against rabies using animal models. Their efficacy was compared to commercially available ERIG both in terms of neutralizing titer and effective protein concentration. The neutralizing titers of these Mabs ranged from 1:10,000 to 1:100,000 by RFFIT. They belonged to the IgG2a subclass. All these Mabs were able to protect 100% of mice and guinea pigs inoculated peripherally with 1,000 LD50 of CVS and street viruses. These Mabs were found to be 2000 times more potent than commercial ERIG in terms of effective protein concentration and neutralizing titer. Further studies are required to study their utility in humans exposed to rabies.

Table showing characterization of Mabs and their neutralizing titres

<table>
<thead>
<tr>
<th>Neutralizing G clones</th>
<th>Isotype</th>
<th>Subtype</th>
<th>Neutralizing antibody titer by RFFIT</th>
<th>In IU/ml</th>
</tr>
</thead>
<tbody>
<tr>
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<td>7500 IU/ml</td>
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Results of time point study for the efficacy of G Mab (2C5E8) in mice using CVS.

Graph showing results of time point study. Note that Mabs are ineffective after 48 hours.
PASSIVE IMMUNIZATION: EXPERIENCE ON EQUINE RABIES IMMUNE GLOBULINS PRODUCED IN INDIA

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Rabies is 100% fatal but preventable by early initiation of proper post exposure prophylaxis. The administration of Rabies immune globulins (RIGs) is life saving in severe (WHO category III) exposures to rabies as vaccine alone would not suffice in these cases. According to WHO-APCRI National Multicentric Indian Rabies survey (2004) 17.4 million animal bite exposures & 20,000 human rabies deaths occur in India & RIGs usage is as low as 2%.

In India, both HRIG and ERIG are available and are used mainly in private sector. HRIG is imported, expensive and scarce and mainly available in bigger cities whereas ERIG is less expensive and is indigenously manufactured both in government & private sector.

An estimated 35,000 litres of RIGs is needed to treat all category III animal bite exposures that occur in the country but only about 5,000 litres of ERIG is being indigenously produced. But even this small quantity of ERIG produced is not being used in the country. The reasons for low use of RIGs are 1) lack of awareness of importance of RIGs both among professionals & public 2) Non availability of RIGs in most parts of the country 3) Non affordability of RIGs by majority of the bite victims 4) Fear of anaphylaxis among professionals 5) Case load and time constraint for administration of RIGs in ARC 6) Lack of trained man power & 7) Apathetic attitude among the professionals. There are many efforts being made to promote RIGs in the country, namely 1) Creating awareness by conducting CME programmes 2) Hands on training in administration of RIGs for both doctors & nursing staff 3) Promoting RIGs as an institutional product 4) Conducting studies on safety & efficacy of ERIG.

Anti Rabies Clinic, Preventive Medicine Unit of KIMS Hospital & Research Center, Bangalore is using all types of RIGs for more than 15 years without any serious adverse reactions. The WHO Premedication protocol for positive skin sensitivity has been modified and being used for more than 3 years.

The following drugs are used based on grading of skin reaction- Inj. Pheneramine Maleate (0.8mg/kg), Inj. Ranitidine (1-2mg/kg), Inj. Hydrocortisone Hemisuccinate (2mg/kg) and Inj. Adrenaline. The ERIGs produced in this country are highly purified, safe & efficacious.
Rabies is fatal viral encephalitis, which is caused by a highly neurotropic, single-stranded RNA virus belonging to the genus Lyssavirus of the family Rhabdoviridae. There are four serotypes in the lyssavirus genus. On the basis of the nucleoprotein gene sequence they can be divided into classical rabies (genotype 1), Lagos bat virus (genotype 2), Mokola virus (genotype 3), Duvenhage (genotype 4), and European bat lyssavirus type 1 and 2 (genotypes 5 and 6, respectively). Australian bat lyssavirus can be distinguished genetically; it is classified as genotype 7, but is serologically closely related to rabies.

Rabies is an important public health problem in South East Asia contributing to about 70% of the global burden. At present, only a few countries in Asia are free of rabies such as Japan, Singapore and Taiwan. India has endured rabies for a long time. A recent national multi-centric survey revealed an annual incidence of 20,565 human deaths due to rabies in India. Rabies is present throughout the country, except on the islands of Lakshadweep, Andaman and Nicobar. Cases are seen throughout the year. In India, rabies is a serious problem because it kills a large number of humans every year. Both sylvatic and urban rabies have been present in India since ancient times. Urban rabies constitutes a dog-to-dog transmission cycle that is maintained in cities. Dogs are the primary source of infection for humans followed by cats and other domestic animals. Rabies epidemiology is highly influenced by human and dog population density, cultural and socioeconomic factors that govern the interaction between those two populations. In contrast, sylvatic rabies is characterized by the involvement of wildlife that maintains stable cycles of transmission over time in particular geographical areas.

In this work we report the first complete genome sequence and characterization of a human isolate of rabies virus from India. The source of the virus was from a tissue section taken from the cerebellum of a 50 year old man who was infected by a bite from a dog five months ago.

The patient developed paralytic rabies manifested as weakness of upper limb and lower limb. The human brain sample was confirmed as rabies by FAT. Total RNA was extracted by using Trizol LS reagent and cDNA was synthesized using different set of primers spanning the rabies virus genome. Total genome was amplified as 13 overlapping PCR products ranging from 521 bp to 2.1 kb. The ends of the genome were amplified by RACE method. The PCR products were cloned into a pGEM-T Easy Vector and sequenced using commercial services. The sequences were analyzed by using Chromas and DNASTAR software. The sequences were compiled by using DNASTAR SeqMan program. The consensus sequence was blasted using NCBI BLAST tool. The sequence matched with AY956319 sequence with 97% homology. The sequence has been submitted to the Gen Bank (Acc. No.EF437215).

Total length of the genome was 11928 nucleotides. It is interesting to note that of the lyssavirus genomes that have been sequenced to date, all have been found to have an even number of nucleotides. This may be a requirement for efficient replication and is equivalent to the paramyxovirus "rule of six". A phylogenetic analysis was also conducted on the complete genome sequence along with complete rabies genome sequences available in the Gen Bank.
Dendrogram (Phylogenetic tree) comparing NIMHANS strain with other strains
In India, modern cell vaccines were introduced in the early 1980's, and from 1995 onwards there has been a significant increase in the use of these vaccines. Presently, almost 60% of rabies exposed people take one of the modern cell culture vaccines and nearly 5 million doses of these vaccines are sold every year. Currently only modern cell cultured vaccines (CCVs) are used for rabies prophylaxis. This paper describes the indigenous development of a chromatographically purified Vero cell rabies vaccine-INDIRAB™, at Bharat Biotech international Ltd, which meets the stringent Indian Pharmacopoeia, European Pharmacopoeia (? 100pg residual cellular DNA/dose)and WHO requirements(? 10ng/dose) for products derived from continuous cell lines. INDIRAB™ is developed from the original Pitman-Moore strain obtained from CDC, Atlanta, USA and derived from the Vero cells, prepared, characterized and validated in USA, meeting US FDA standards. This study was done to assess the immunogenicity (Efficacy) and safety of INDIRAB™ in comparison to the reference Purified Vero cell Rabies Vaccine (PVRV) available in the market. Healthy volunteers from 2 centers (Hyderabad & Bangalore) were recruited for the study. They were administered INDIRAB™ and reference PVRV by intramuscular route using Essen regimen for Pre & Post Exposure Prophylaxis. The subjects were followed for 3 months and adverse reactions were recorded. Antibody titers were estimated by Rapid Fluorescent Focus Inhibition Test (RFFIT) at NIMHANS, a WHO approved centre, Day 14, Day 28 and Day 90 post vaccination. The Geometric mean titers on different days for INDIRAB™ and reference PVRV are shown in the Table-1.

Table-1. Geometric Mean Titre (GMT) of serum neutralizing antibodies following post-exposure immunization with INDIRAB™ and Reference PVRV.

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>GMT on Day 14</th>
<th>GMT on Day 28</th>
<th>GMT on Day 90</th>
</tr>
</thead>
<tbody>
<tr>
<td>INDIRAB™</td>
<td>5.5</td>
<td>11.5</td>
<td>8.5</td>
</tr>
<tr>
<td>Reference PVRV</td>
<td>5.3</td>
<td>11.2</td>
<td>9.0</td>
</tr>
</tbody>
</table>

None of the subjects had neutralizing antibody titers on day "0". All subjects in both the groups developed antibodies which were significantly greater than the protective titers of 0.5IU. INDIRAB™ showed similar general vaccine related symptoms as that of reference PVRV, with systemic reactions at a lower end due to removal of impurities that were thought to be responsible for systemic reactions during the manufacture through chromatographic technique.
To conclude, this study has shown that INDIRAB™ is Safe, Immunogenic and efficacious as compared with a reference PVRV available in the Indian market. Therefore, INDIRAB™ is a valuable addition to the rabies vaccine arsenal towards a rabies free India.

Graph showing antibody response to INDIRAB™ in healthy volunteers

Graph showing antibody response to INDIRAB™ compared to a control vaccine
Efficacious vaccines and immunoglobulins are one of the best ways to control human rabies. Modern cell culture and embryonated egg derived vaccines have dramatically decreased human rabies deaths worldwide, most notably where canine rabies is endemic.

Developed in 1984, purified Vero cell culture rabies vaccine (PVRV, Verorab™, Sanofi Pasteur, France) has been used for over 20 years with more than 75 million doses administered in 150 countries throughout Europe, Asia, Africa and Latin America.

Verorab™ is the most widely used WHO recommended cell-culture rabies vaccine with demonstrated efficacy and safety in pre-and post-exposure prophylaxis by intramuscular (IM) or intradermal (ID) routes.

In addition to their usual IM administration, the WHO recommend certain reduced dose, ID regimens which are of interest in areas where rabies vaccines are in short supply and resources are limited. ID regimens could offer an alternative solution for post-exposure prophylaxis in countries where outdated nerve-tissue vaccines are still produced and used.

The implementation of ID post-exposure prophylaxis is the responsibility of the national authorities in charge of rabies prevention and treatment. Local manufacturers in rabies endemic countries are beginning to produce cell culture vaccines which may be candidates for ID regimens. However, not only must they meet the same quality, safety and efficacy specifications defined by WHO for the production and control of IM vaccines but they must also comply to WHO standards for ID administration if they are to be recommended by WHO. Three major issues must be addressed for all vaccines considered for ID administration: the antigen content of the reduced dose must be confirmed and sufficient to secure immunogenicity, the lack of preservative in the vaccine vial may pose problems if used for several injections without using a specific product handling protocol, and there is a need for well trained, qualified personnel to perform ID injections. Any failure to address these issues may put patients' lives at risk. To this end, clinically documented proof of their safety and effectiveness when given ID must be provided before vaccines are approved by national health authorities. In view of these constraints, only a limited number of rabies vaccines are recognized by the WHO as safe and efficacious for ID post-exposure prophylaxis.

Verorab™ has been approved for both "Thai Red Cross" (TRC) and "updated TRC" regimens by the WHO. Studies on PVRV in ID regimens began in the late 1980s and it was approved by the WHO for the TRC regimen in post-exposure prophylaxis in 1996. Several clinical and field effectiveness trials on ID administration of Verorab™ in different pre- and post-exposure schedules have been carried out on over 4,000 subjects including pregnant women, children, and high-risk patients with severe wounds from confirmed rabid animal. PVRV rapidly and consistently elicted neutralizing anti-rabies antibody levels detectable after 7 days in all regimens. The accepted protection threshold (0.5 IU/mL measured by RFFIT) was surpassed 21 to 28 days after two doses in pre-exposure studies, and 14 days after three doses in post-exposure studies.

Thus, two decades of extensive clinical experience supports the efficacious and safe use of PVRV, Verorab™ for IM and ID pre- and post-exposure prophylaxis of human rabies.
**Table showing efficacy of Verorab™ in different studies**

<table>
<thead>
<tr>
<th>Year</th>
<th>Location</th>
<th>Proven cases bitten by rabid dogs</th>
<th>Vaccination schedule</th>
<th>Follow-up period</th>
<th>Survival rate %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1986</td>
<td>Thailand</td>
<td>106</td>
<td>0.5 ml IM on days 0, 3, 7, 14, 28 and 91 with or without HIG</td>
<td>1 year</td>
<td>100%</td>
</tr>
<tr>
<td>1988</td>
<td>Thailand</td>
<td>309</td>
<td>0.5 ml IM on days 0, 3, 7, 14, 30 and 90 or 0.1 ml TRC-ID, with HIG for Category III exposure</td>
<td>3 months and 1 year</td>
<td>100%</td>
</tr>
<tr>
<td>1994</td>
<td>India</td>
<td>52</td>
<td>IM ESSEN + RIG</td>
<td>25 months</td>
<td>100%</td>
</tr>
<tr>
<td>1996</td>
<td>Thailand</td>
<td>84</td>
<td>IM ESSEN + RIG (x=44)</td>
<td>3 years</td>
<td>100%</td>
</tr>
<tr>
<td>2000</td>
<td>China</td>
<td>171</td>
<td>IM ESSEN + ERIG+RIG</td>
<td>6 months</td>
<td>100%</td>
</tr>
</tbody>
</table>

*VERORAB™ 100% Survival rate in PET*

*Effectiveness of VERORAB™ demonstrated in different field studies with 100% survival rate after bitten by rabid animals*


**PANEL DISCUSSION**

Dr. Madhusudana, the chairperson of RIACON welcomed the gathering to the panel discussion and invited Dr. Deborah Briggs to moderate the discussion. He invited the panelists, Dr. Meslin, Dr. Sudarshan, Dr. Ichhpujani, Dr. Abdul Rahman, Dr. Naseem Salahuddin, Dr. Henry Wilde and Dr. Yong Zhen Zhang to the stage and hoped that a fruitful and meaningful discussion will take place during the session.

Dr. Briggs thanked the organizers for having given the opportunity to moderate this session and began the discussion with Dr. Meslin.

**Dr. Briggs:** I would like to begin the discussion by asking a question to Dr. Meslin. I would like to ask him how can WHO interact with RIA and its member countries more effectively?

**Dr. Meslin:** WHO has always been supporting the cause of rabies control in Asian countries. It has played a key role in formation of RIA and has been collaborating with Dr. Sudarshan and others in organizing this meeting. The WHO will certainly follow the activities of RIA and offer assistance in whatever way it can. We have made a beginning in bringing together so many experts from Asia and I certainly like to see periodic meetings of rabies experts from Asia and WHO will be a part of all such activities.

**Dr. Briggs:** Dr. Sudarshan, as President of RIA what are your future plans as far as the functioning of RIA is concerned?

**Dr. Sudarshan:** First of all I thank Dr. Meslin for giving assurance for continued support from WHO for the activities of RIA. Similarly I would solicit full cooperation from all member countries in working together to eliminate human rabies form Asian Countries. A beginning has been made and this should be followed by more activities from all member countries. We have already identified the chairpersons of individual country chapters and I request them to give their full support to all RIA activities. We have to
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decide about the date and venue of the next RIACON. This can be decided in the RIA official meeting which will be held after the panel discussion. Soon World Rabies day will be observed and I request all member countries to organize meaningful activities on this occasion.

Dr. Briggs: Thank you Dr. Sudarshan. As the most pressing question for rabies control in Asian countries is the control of rabies in dog population, I would like to have the opinion of Dr. Abdul Rahman in this regard.

Dr. Rahman: In my opinion dog population control should be given top most priority as more than 95% of human deaths are due to dog bites. The ABC programme operational in some countries should be intensified and introduced in countries where it is not presently operational. In this regard, professional bodies such as APCRI, RIA, CVA and OIE should join hands and work together.

Dr. Briggs: I will now like to have the opinion of Dr. Naseem from Pakistan as I gather that recently Pakistan has taken up a lot of initiatives in public education about rabies.

Dr. Naseem: Thank you Debbie. Yes, in my opinion education and increasing awareness about rabies is pivotal in for any rabies control programme to be successful. The education should start at grass root level. Start educating children, parents, Medical professionals and paramedics. Then move to provincial and central governments. In Pakistan, a major constraint is the lack of human resources and laboratory facilities for the diagnosis of animal and human rabies. This should be improved. I hope that RIA will take some initiative in helping member countries to improve their laboratory facilities.

Dr. Briggs: Moving now to China, where rabies deaths have increased significantly I request Dr. Zhang to give his opinion.

Dr. Zhang: In China increasing public awareness has been a top priority. It is almost complete in major cities and urban areas. It needs to be improved in rural areas. In any government programme cooperation of people is equally important and I am glad that people are actively involved and they are now more educated about the rabies situation and more number of people are taking treatment. I do hope that in near future there will be reduction in number of rabies deaths in China.

Dr. Briggs: Dr. Ichhpujani, you represent the Government of India and as you know highest number of deaths are from India. Do you have any suggestions as to how RIA should interact with government in future to reduce the burden of rabies in India?

Dr. Ichhpujani: I visualize the role of RIA in a different way. Obviously RIA cannot function independently without involving respective governments. RIA should find ways to educate government on the continued rabies deaths which are preventable. It is high time that a national rabies control programme be implemented. RIA, APCRI and other NGOs should actively participate in such programmes.

Dr. Sudarshan: I want to again place on records the valuable support and assistance given by Dr. Meslin and WHO for organizing this meeting and future assurance that WHO will continue to support the activities of RIA. I agree with Dr. Ichhpujani. We have to tackle the problem at highest level. If it clicks there it clicks everywhere. We have to educate our ministers as we did for the implementation of ID route of vaccination. We have to submit a memorandum to the health minister requesting him to give rabies a priority and implement national control programme.

Dr. Wilde: I recall Dr. Omala when she worked with us as a WHO fellow, telling me that instead of educating doctors I am going to educate people. If people are aware of the threat of rabies, they force the doctors to give proper treatment. This is what Dr. Thawachai also did in his province at Thailand. I feel, overall educating people should be given top priority.

Dr. Briggs: Dr. Omala, you are source of inspiration to so many people. Tell me how could you manage as a one woman army, change the scene in Sri Lanka and create such a good awareness about rabies?
Dr. Omala: First of all, I realized that educating people is far more rewarding than educating medical professionals. Fortunately, the literacy rate in Sri Lanka is very high, almost 90%. The people are health conscious. I started from school children, their parents and teachers. I visited more than 300 schools all over Sri Lanka. I got support from my colleagues specially Dr. Harischandra and most importantly I could convince my government and got sufficient funds for the activities. Now I have trained several of my juniors who will take the responsibility of sustaining the activities.

Dr. Rahman: I fully agree with Dr. Omala. Public awareness cannot be increased without the full support of government. Policy makers, ministers and bureaucrats should be made aware of the situation that so many rabies deaths are happening because of ignorance. In one of the meetings I was surprised that a minister for external affairs was surprised by the rabies figures we gave him and he immediately offered money to publish a document on this. What I want to stress again is that we need to educate our own ministers and particularly bureaucrats.

Dr. Yathiraj: I like to add that there is lack of awareness among pet dog owners as well. I am surprised that only about 40% of pet dogs are vaccinated regularly and in any antirabies clinic, nearly 60% of cases are due to pet dog bites. There is an urgent need to increase awareness even among pet dog owners.

Dr. Briggs: Continuing the discussion on role of public education, I would now like to have the opinion of major vaccine manufacturers.

Mr. R. K. Suri: From our side (Sanofi Pasteur) we have a three-pronged approach. We have always stood behind giving financial and moral support to academic forums such as APCRI and RIA and I am happy to say that these bodies have done a good amount of work in the past few years. We have a very strong field force which percolates in to the remote village level and we have enhanced public awareness through CME programmes not only in major cities but even at district levels. Even before the banning of NTV by the central government, we on our own have as far as possible encouraged the use of TCV by highlighting the drawback of NTVs. We have been instrumental in advocating pre-exposure vaccination particularly in children.

Dr. Claudius: I want to reiterate what the previous speaker has said. As a major vaccine manufacturer we have always stood behind rabies experts all over the world, particularly in India and other Asian countries. We have financed and will continue to finance need based research and clinical trials. We have particularly supported ID trials, and we are now supporting trials on pre-exposure vaccination of children in many countries. We have made an educative film on rabies which is being shown in many countries.

Dr. Bourhy: I am not from the industry but I like to share with you that Institut Pasteur has conducted several training programmes on rabies in Asian countries such as China, Vietnam, Laos and Cambodia.

Dr. Wilde: I once again raise the same issue. With out the support of the local governments it is not possible to achieve anything. Look at countries like Japan, Singapore, Taiwan and Malaysia. How did they achieve rabies free status? The government in these countries eliminated stray dogs, encouraged responsible pet ownership and strict licensing and compulsory pet vaccination. We need to follow such examples from the past and more recently we should look at the success stories of Sri Lanka and Thailand where there is active involvement of the respective governments. It is high time, that India learns lessons from these countries.

Dr. Vakil: I wholeheartedly agree that public education is the key factor. The success of the programme depends on the population of the country. It may be relatively easier in small countries like Sri Lanka or Thailand. But when it comes to a country like India where population is over one billion, things become difficult and time consuming before at least 50% of the country's population becomes rabies-educated. I want to reiterate that the private sector is doing a lot in this field and a good vaccine has been made available even at taluk levels.
Dr. Ichhpujani: We did propose to government of India to allot funds for control of rabies during 10th five-year plan but it was turned out. I am glad to inform you that in the 11th 5 year plan funds have be allocated to rabies and we are planning to have pilot projects for rabies control in some selected cities of India.

Dr. Briggs: As we are running short of time I want to wind up the discussion. The summary of the whole discussion is that increasing public awareness is the key factor which should be addressed immediately and we are having a very good platform to do this when we observe World Rabies Day on September 8th. We should use this opportunity to come out with meaningful strategies, convince policy makers in respective governments and also make public aware that nobody need die of rabies as tools for its prevention are available and should be used as and when required. I also gather from the discussion it takes only one person to change the scenario as it happened in Sri Lanka and as it is now happening in Pakistan. I thank my panelists for active participation and also the people from audience who gave their views and enriched the discussion.
CONCLUSIONS AND RECOMMENDATIONS

The two day conference of the Rabies in Asia (RIA) Foundation, after successful deliberations, came out with following conclusions and recommendations. It is expected that the health policy makers of the Asian countries where rabies burden is still on higher side, follow these recommendations and evolve strategies that eventually reduce or eliminate human rabies deaths.

CONCLUSIONS

- Over the past 10 years mortality from rabies has decreased significantly in a number of Asian countries such as Thailand, the Philippines and Sri Lanka. The situation has however deteriorated in certain other Asian countries such as China, with an increased number of human deaths and an expansion of the disease to previously free areas reported during that period.

- Rabies continues to be a significant problem in India, Pakistan and Bangladesh, which altogether represent more than 70% of all rabies deaths reported in Asia.

- Decreases in mortality data have been the result of strengthened activities in both the human and animal sectors in Thailand and Sri Lanka. In both countries however a large part of the improvement is due to increased patient access to post-exposure prophylaxis and public awareness of the disease.

- Modern cell culture vaccines whether locally produced or imported are now available at least through the private sector, in major urban centres of all Asian countries. Modern vaccine consumption in Asia has more than doubled over the past 10 years with an estimated 10 million post-exposure prophylaxis (PEP) regimens provided each year. It was noted that some countries are still reporting human rabies deaths in spite of providing 3 to 4 times more PEP per million than estimated necessary (2000 PEP per million) to prevent all human deaths in that population.

- A major improvement in the region in recent years has been the complete discontinuation of the production and use of brain tissue derived vaccine in India (December 2004) and Nepal (December 2006). Brain tissue vaccines are still in used in Bangladesh and Pakistan.

- Furthermore in many countries modern vaccine availability for PEP has been increased through the use of economical intradermal regimens. The intradermal route has become the most frequently used route for PEP administration in Sri Lanka and the Philippines and to a lesser extent in Thailand. Intradermal application of rabies vaccines for PEP has been recently introduced in India and Pakistan.

- Political commitment to human and dog rabies control remains limited in most countries. Availability of resources for rabies prevention and control has been affected in certain countries by priority diseases (e.g. HIV/ AIDS, TB). Rabies Committees in some countries have developed long term plans for human and dog rabies control and set a date for rabies elimination. For example, Philippines aim at 2020 and Sri Lanka 2018.

RECOMMENDATIONS

1. Human rabies prevention and control:

- Vaccine and RIG availability: Access to modern vaccine for PEP has increased in all countries of the region. However, they are not accessible to the poorest segment of the population. It is recommended that:

  - Modern rabies vaccines are made freely available to this population in all countries of the region.

  - To reduce the cost, the use of the intradermal route should be implemented in all public hospitals.
and bite treatment centres serving poor populations.

RIGs are in short supply in all countries of the regions and it is acknowledged that the proportion of exposures that would require their use is much higher (65%) than initially thought. National production of ERIG should be strengthened. As cost of RIG represent 2/3 of the total cost of a full PEP regimen to be provided in category 3 exposure RIG should also be made available for free for the poor patients. To improve compliance with WHO recommendations for proper PEP delivery in category III exposure, WHO is requested to develop a guide for RIG administration. WHO project for the production of a monoclonal antibodies cocktail as an alternative to RIG shortage should be accelerated and the further support from all the WHO/CC involved, WHO Headquarters and potential industrial partners is requested by the meeting.

Pre-exposure immunization of vulnerable population:

Experiences from the Philippines and Thailand shared at the occasion of this meeting indicate that preventive immunization of school children by the intradermal route is feasible and may help offset problems of immunoglobulin shortage when a vaccinated child is exposed. As children represent most of the dog rabies victims voluntary and/or government sponsored immunization of children should be promoted in all areas where dog rabies is present.

Human rabies diagnosis and surveillance:

Laboratory confirmation of suspect/probable cases of rabies in humans should be attempted whenever possible. All PEP failures or suspected failures should be reported to relevant Ministry of Health and the WHO Geneva as soon as possible using the following email rabnet@who.int. A questionnaire can be developed using model given as annex 5 of the Report of the WHO Expert Consultation on Rabies, TRS 931, WHO 2005. Viruses from these cases should be isolated and characterized.

Human rabies should become a notifiable disease in all countries of the region. Human rabies cases (whether probable, suspected or confirmed) should be reported in RABNET (at www.who.int/rabnet) at least annually. Country representatives will contact the relevant officer in the Ministry of Health for that purpose.

Dog rabies control and dog population management:

Dog rabies control:

Dog rabies control activities are weak in most countries and do not reach the targeted coverage of 75%. Dog rabies control through immunization is the most cost effective single measure available.

- It is therefore recommended that Asian countries mobilize additional resources to strengthen their dog rabies immunization activities.

- In many Asian countries the size, structure, turnover of the dog population is not known.

- Conducting small-scale dog population studies in as many representative parts of a given country as possible is recommended. Protocols for dog population studies are available from WHO.

When in an area a large segment of the dog population has been shown to be inaccessible to parenteral immunization the use of the oral route for dog immunization should be considered. Vaccine candidates should have fulfilled WHO safety and efficacy requirements for such product in a bait. Protocols for testing candidate dog bait-vaccines and assessing risk of human exposure and bait distribution method are available from WHO. In addition, laboratory confirmation of all suspect rabid dogs should become an integral part of the programme. Efforts should be made to increase diagnostic facilities and trends in the incidence of dogbites should be monitored to evaluate the success of dog vaccination programmes.
Dog population management:

Dog population management is an integral part of a dog rabies control programme. It is recommended that dog population management strategies comply with animal welfare principles. Removal of certain dogs (sick, rogue) is an important way of protecting dog and human populations in a given area. It is recommended that aggressive dogs are identified through frequent observations of community/village dog populations and removed from these populations as soon as possible. These animals should be isolated and dealt with in a humane manner.

National plans for rabies control

Rabies Committees in some countries have developed long term plans for human and dog rabies control and set a date for rabies elimination. It is recommended that all countries of the region where these do not exist yet, set up their inter-sectoral rabies committee. These committees should develop a national plan with clear quantifiable objectives. The designation of a National Programme Director is an essential component of success. The Committee may take the help of WHO collaborating centres present in the region for formulating national guidelines for prevention and control of rabies and also for diagnosis and epidemiological surveys for human and animal rabies. Periodic training programmes should be arranged with the help of this WHO CC for training of medical officers and laboratory technicians in diagnosis of rabies and proper management of post-exposure cases. In addition, public education about consequences of dog bites and their management should form an integral part of national programmes. Information (in as simple way as possible) should be provided to people through mass media such as TV, radio, newspapers, periodicals and Internet.

In addition, it is also suggested that each country in the region should assess specific problems peculiar to that country and work out strategies to overcome the same. The countries can take the help of WHO in formulating such strategies.
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