APEC CONFERENCE

for the Surveillance, Treatment, Laboratory Diagnosis and Vaccine Development of Enteroviruses

DATE
13-14 August 2009
VENUE
Taipei International Convention Center
ORGANIZER
Centers for Disease Control
Chinese Taipei

APEC
Asia-Pacific Economic Cooperation

Centers for Disease Control

APEC Project HTF 01/2009A

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Welcome Message

Welcome to the APEC Conference for the Surveillance, Treatment, Laboratory Diagnosis and Vaccine Development of Enteroviruses.

Enterovirus has recently become an issue of great concern among many APEC economies. Humans are the only known natural hosts for enterovirus and young children are most susceptible to the infection. Outbreaks of hand-foot-mouth disease associated with enterovirus infection have previously been reported in several APEC member economies. The number of severe enteroviral infection continues to increase yearly. In addition, no preventive vaccines and efficacious medicine are currently available to eliminate these viruses.

The purposes of this conference are to share our own experiences and to improve the capacity of APEC members in enterovirus infection control. Moreover, the theories and practices related to the control and prevention of enteroviruses will be introduced during the conference. The conference will provide a good opportunity for all APEC member economies to exchange and share experience and information in controlling and preventing enteroviruses.

I hope you will find this conference enjoyable and productive. Thank you all for your participation and contributions to this event, and I wish you have a wonderful time in Taipei.

Steve H.S. Kuo, MD, MPH, PhD
Project Overseer
APEC Conference for the Surveillance, Treatment, Laboratory Diagnosis
and Vaccine Development of Enteroviruses
Director
Centers for Disease Control
Chinese Taipei

Conference Information

Date

13-14 August 2009

Venue

Taipei International Convention Center
4th Floor VIP Room
Address: No.1, Hsin-Yi Road, Sec. 5, Taipei 11049, Taiwan
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Organizer

Centers for Disease Control, Chinese Taipei

Official Language

English


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Chung-hsiao East Road, Sec. 5
Taipei City Hall Station
S.Y.S.Memorial Hall Station
Sung-Kao Road
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Xiao-ning Road, Sec. 1
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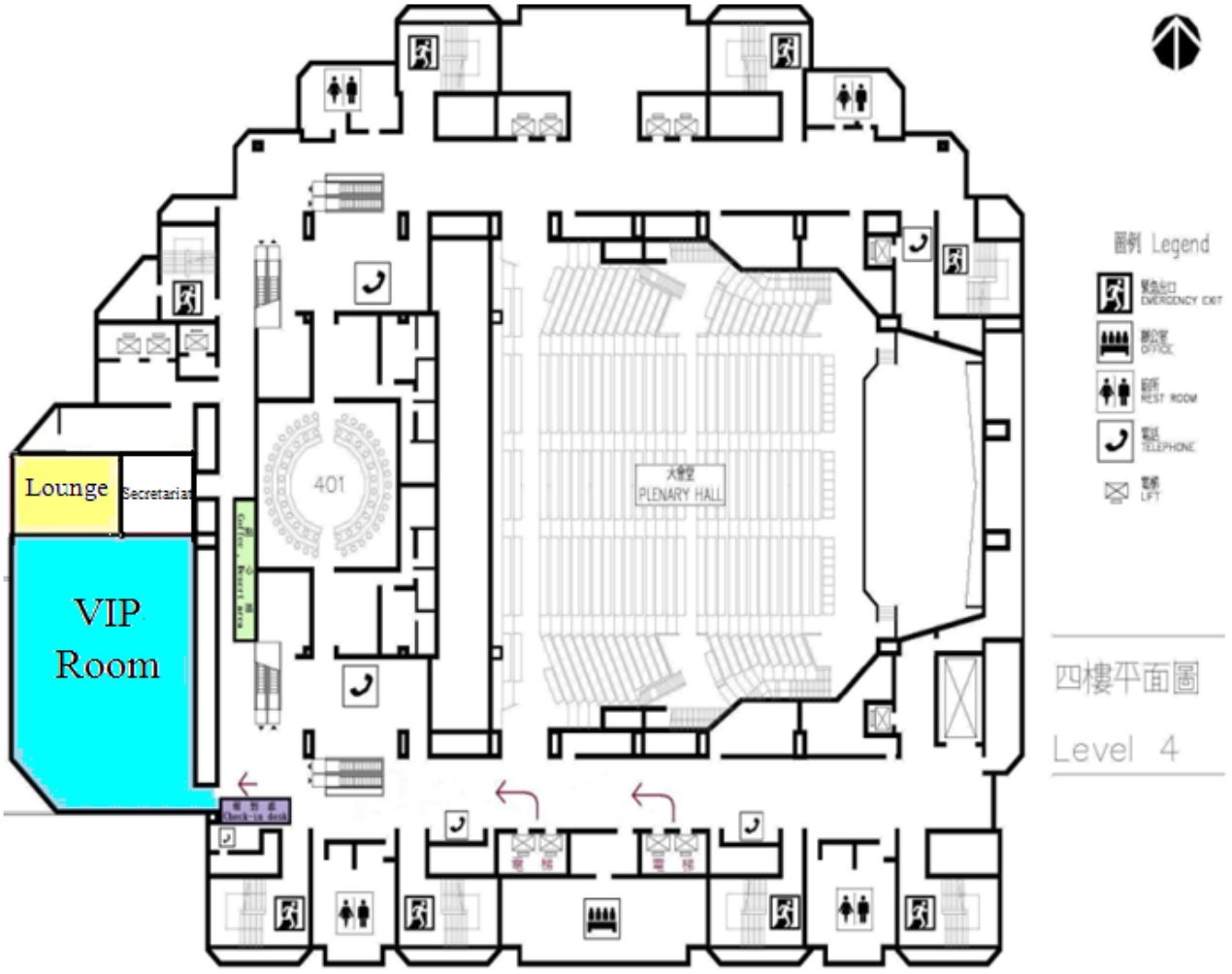
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REST ROOM
TELEPHONE
LIFT
四樓平面圖
Level 4

Opening Ceremony

Tzay-Jinn Chen, MD, MPH

Current Position: Deputy Minister
Organization: Department of Health (DOH), Chinese Taipei
Economy: Chinese Taipei

Education

- MPH, 1991, Harvard University, School of Public Health, Boston, MA, USA
- MD, 1976, National Taiwan University, College of Medicine, Chinese Taipei

Professional Experiences

- Deputy Minister, Department of Health (DOH), Chinese Taipei, August 2004-Present
- Director-General, Hospital Management Commission, DOH, 2003-2005
- Director-General, Center for Disease Control, DOH, 2002-2003
- Director-General, Bureau of Health Promotion & Protection, DOH, 1998-2001
- Superintendent, Taipei City Ho-Ping General Hospital, 1995-1997

Professional Specialties

- Hospital Administration and Quality Management
- Specialties in Medicine: Chest and Critical Medicine, Nephrology, Internal Medicine, Occupational Medicine
- Public Health: Health Promotion and Protection, Infectious Disease Control, Medical Regulation and Law

Steve Hsu-Sung Kuo M.D., MPH, PhD

Dr. Steve Kuo is currently the Director of Centers for Disease Control. Born in 1957, Dr. Kuo was raised and completed his pre-college education in Taipei. He received MD degree in 1982 from National Yang-Ming Medical College, MPH degree from National Taiwan University. in 1984, and a PhD degree on health policy from Yale University 1991.

From 1991 to 1998, Dr. Kuo held various positions in the National Yang-Ming University including Associate Professor, Director of Department of Social Medicine, Associated Dean of Faculty of Medicine, Secretary-General, and the founding director of the Institute of Health Informatics and Decision Making. He taught and studied in areas of policy modeling, cost-effectiveness evaluation, and healthcare ethics. Currently he is an adjunct professor of the University.

In 1998, he moved to Health Ministry and served as the Director-General of the Bureau of Planning and Evaluation where he initiated many major projects, such as reforming CDC, establishing the National Institute of Health Promotion, and National Health Information Network 2.0, before he moved to Washington D.C. for a newly created position in July, 2002.

From 2002 to 2004, Dr. Kuo was the health advisor of Taipei Economic and Cultural Representative Office (TECRO), Washington DC. His primary responsibility is to enhance the bilateral exchange in health affairs and to promote our standing in the arena of international health. During the SARS outbreak in Spring of 2003, Dr. Kuo returned to Taipei and served as the Chief Coordination Officer and Spokesman of the SARS Task Force. He served the position till the outbreak was brought under control in June, 2003. He was promoted to the current position in 2004.

He plays golf and badminton, and enjoys mountain climbing and travel.

Session I：Epidemiology & Public Health

Moderator：

Dr. Henry Baggett, Chief, Epidemiology Section, International Emerging Infections Program-Thailand, Global Disease Detection Network, Southeast Asia Regional Office, U.S. Centers for Disease Control and Prevention.

Dr. Jih-Haw Chou, Deputy Director, Centers for Disease Control, Chinese Taipei

Speaker：

Dr. David Perera, Deputy Director, Institute of Health & Community Medicine, University Malaysia Sarawak, Malaysia

Dr. Sue Huang, Head, National Poliovirus and Enterovirus Reference Laboratory, Institute of Environmental Science and Research, National Centre for Biosecurity and Infectious Disease, New Zealand

Ms. Ding-Ping Liu, Director, Division of Acute Infectious Diseases & Immunization (2nd Division), Centers for Disease Control, Chinese Taipei

Dr. Henry Baggett

Current Position: Section Chief
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Educational Background

- MD – University North Carolina
- MPH – University Washington
- Pediatrics Residency – Johns Hopkins Children's Hospital

Professional Career

Has served as Epidemiology Section Chief for the U.S. CDC's International Emerging Infections Program in Thailand since November 2006, where much of his work has focused on the burden of respiratory diseases, including Streptococcus pneumoniae. He has also supported outbreak response and planning for hand, foot, and mouth disease/enterovirus 71 in the region.

Dr. Baggett completed his medical degree at the University of North Carolina and Pediatrics training at Johns Hopkins Children's Hospital in Baltimore. He started with CDC in 2000 as an EIS officer with the Arctic Investigations Program in Anchorage, Alaska, where much of his work focused on the epidemiology and risk factors for community-associated MRSA. He subsequently received an MPH in epidemiology from the University of Washington in Seattle and completed CDC's Preventive Medicine Residency. He is board certified in pediatrics and general preventive medicine.

Publications

- Incidence of pneumococcal bacteremia requiring hospitalization in rural Thailand.Baggett HC, Peruski LF, Olsen SJ, Thamthitiwat S, Rhodes J, Dejsirilert S, Wongjindanon W, Dowell SF, Fischer JE, Areerat P, Sornkij D,

Jorakate P, Kaewpan A, Prapasiri P, Naorat S, Sangsuk L, Eampokalap B, Moore MR, Carvalho G, Beall B, Ungchusak K, Maloney SA. Clin Infect Dis. 2009 Mar 1;48 Suppl 2:S65-74.

- Epidemiology of radiographically-confirmed and bacteremic pneumonia in rural Thailand.Prapasiri P, Jareinpituk S, Keawpan A, Chuxnum T, Baggett HC, Thamathitiwat S, Olsen SJ.Southeast Asian J Trop Med Public Health. 2008 Jul;39(4):706-18.
- Bartonella tamiae sp. nov., a newly recognized pathogen isolated from three human patients from Thailand. Kosoy M, Morway C, Sheff KW, Bai Y, Colborn J, Chalcraft L, Dowell SF, Peruski LF, Maloney SA, Baggett H, Sutthirattana S, Sidhirat A, Maruyama S, Kabeya H, Chomel BB, Kasten R, Popov V, Robinson J, Kruglov A, Petersen LR.J Clin Microbiol. 2008 Feb;46(2):772-5. Epub 2007 Dec 12.
- Two nosocomial pertussis outbreaks and their associated costs - King County, Washington, 2004. Baggett HC, Duchin JS, Shelton W, Zerr DM, Heath J, Ortega-Sanchez IR, Tiwari T. Infect Control Hosp Epidemiol. 2007 May;28(5):537-43. Epub 2007 Mar 22.
- Immunologic response to Haemophilus influenzae type b (Hib) conjugate vaccine and risk factors for carriage among Hib carriers and noncarriers in Southwestern Alaska.
  Baggett HC, Hennessy TW, Bulkow L, Romero-Steiner S, Hurlburt D, Holder P, Parkinson AJ, Singleton RJ, Levine O, Carlone GM, Butler JC. Clin Vaccine Immunol. 2006 Jun;13(6):620-6.

Dr. Jih-Haw Chou

Current Position: Deputy Director
Organization: Centers for Diseases Control
Economy: Chinese Taipei
Tel: + 886 2 2394 5203
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Educational Background

- MPH (Environmental Toxicology), University of California at Berkeley.
- MPH (Epidemiology), National Taiwan University, Chinese Taipei
- DDS, Taipei Medical College.

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Publications

- Health Commissioner, Taipei County Health Department.
- Deputy Health Commissioner, Taipei County Health Department.
- Director, Div. Research, Planning and Development, Taipei City Health Department.
- Branch Chief, National Quarantine Service.
- Specialist, Bureau of Communicable Disease Control.

Dr. David Perera

Current employment: Deputy Director
Organization: Institute of Health and Community Medicine, University Malaysia Sarawak
Economy: Malaysia
Tel: 082-67100 ext 2301
Email: davidperera@yahoo.com

Education

- 1992 Graduated with B.Sc. (Hons.), majoring in Biotechnology with a minor in computer science.
- 1998 Graduated with M.Sc. (Molecular biology) Thesis: Characterization of origin of replication sites of plasmids from *Bacillus thuringiensis* var *aizawai*.
- 2005 Graduated with Ph.D. (Medical biotechnology) Thesis: Characterization of an unusual adenovirus strain, SIBU97.

Research interests

Flavivirus and enterovirus pathogenesis and epidemiology.
Viral diagnostics.

Awards

- Post-graduate and Post-doctoral fellowship (PTPTP) research award (1997-2000).
- Nasional Science Foundation Scholarship, Kementerian Sains, Teknologi dan Alam Sekitar (2000-01).
- Research Officer/Post-Doctoral Fellowship funded by "International Collaborative Research Grant – Enterovirus 71 in the Asia-Pacific Region: Reverse genetic approaches to virus surveillance and vaccine development (2004-2007)

Publications

- Holmes, EC, Tio, P-Hc, **Perera, D**, Muhi, J, Cardosa, MJ (2009). Importation and co-circulation of multiple serotypes of dengue virus in Sarawak, Malaysia. *Virus Res*. **143**:1-5.
- Cardosa J, Ooi MH, Tio PH, **Perera D**, Holmes EC, Bibi K, Abdul Manap Z (2009). Dengue virus serotype 2 from a sylvatic lineage isolated from a patient with dengue hemorrhagic Fever. *PLoS Negl Trop Dis*. **3**(4):e423

- Ooi MH, Wong SC, Mohan A, Podin Y, **Perera D**, Clear D, del Sel S, Chieng CH, Tio PH, Cardosa MJ, Solomon T (2009). Identification and validation of clinical predictors for the risk of neurological involvement in children with hand, foot, and mouth disease in Sarawak. *BMC Infect Dis*. 9:3.
- Zaki A, **Perera D**, Shahrina SJ, Cardosa MJ (2008). Phylogeny of dengue viruses circulating in Jeddah and Meccah, Saudi Arabia: 1994 to 2006. *Tropical Medicine & International Health* **13**:1-9.
- Tu PV, Thao NTT, **Perera D**, Khanh TH, Tien NTK, Thuong TC, Ooi MH, Cardosa MJ, McMinn P (2007). Epidemiologic and virologic investigation of hand, foot, and mouth disease, southern Vietnam, 2005. *Emerging Infectious Diseases* **13**:1733-1741.
- **Perera D**, Yusof MA, Podin Y, Ooi MH, Thao NTT, Wong KK, Zaki A, Chua KB, Malik MA, Tu PV, Tien NTK, Puthavathana P, McMinn PC, Cardosa MJ (2007). Molecular phylogeny of modern coxsackievirus A16. *Archives of Virology*, online publication.
- Ooi MH, Solomon T, Podin Y, Mohan A, Akin W, Yusof MA, del Sel S, Mohd Kontol K, Lai BF, Clear D, Chieng CH, Blake E, **Perera D**, Wong SC, Cardosa MJ (2007). Evaluation of different clinical sample types in the diagnosis of human enterovirus 71 associated hand, foot and mouth disease. *Journal of Clinical Microbiology* **45**:1858-1866.
- Ooi MH, Wong SC, Podin, Y, Akin W, del Sel S, Mohan A, Chieng CH, **Perera D**, Clear D, Wong D, Blake E, Cardosa MJ, Solomon T (2007). Human enterovirus 71 disease in Sarawak, Malaysia – a prospective clinical, virological and molecular epidemiological study. *Clinical Infectious Diseases* **44**:646-656.
- Podin Y, Gias EL, Ong F, Leong YW, Yee SF, Yusof MA, **Perera D**, Teo B, Wee TY, Yao SC, Yao SK, Kiyu A, Arif MT, Cardosa MJ (2006). Sentinel surveillance for human enterovirus 71 in Sarawak, Malaysia: lessons from the first 7 years. *BMC Public Health* **6**:180.
- **Perera D**, Podin Y, Akin W, Tan CS, Cardosa MJ (2004). Incorrect identification of recent Asian strains of Coxsackievirus A16 as human enterovirus 71: improved primers for the specific detection of human enterovirus 71 by RT PCR. *BMC Infectious Diseases*. **4**:11.
- Cardosa MJ, **Perera D**, Brown BA, Cheon D, Chan HM, Chan KP, Cho H, McMinn P (2003). Molecular epidemiology of human enterovirus 71 strains and recent outbreaks in the Asia-Pacific region: comparative analysis of the VP1 and VP4 genes. *Emerging Infectious Diseases*. **9**:461-8.
- Ooi MH, Wong SC, Clear D, **Perera D**, Krishnan S, Preston T, Tio PH, Willison HJ, Tedman B, Kneen R, Cardosa MJ, Solomon T (2003). Adenovirus type

21-associated acute flaccid paralysis during an outbreak of hand-foot-and-mouth disease in Sarawak, Malaysia. *Clinical Infectious Diseases*. **36**:550-9.

- McMinn P, Lindsay K, **Perera D**, Chan HM, Chan KP, Cardosa MJ (2001). Phylogenetic analysis of enterovirus 71 strains isolated during linked epidemics in Malaysia, Singapore, and Western Australia. *Journal of Virology.* **75**:7732-8.
- Cardosa MJ, Krishnan S, Tio PH, **Perera D**, Wong SC (1999). Isolation of subgenus B adenovirus during a fatal outbreak of enterovirus 71-associated hand, foot, and mouth disease in Sibu, Sarawak. *Lancet.* **354**:987-91.

A Decade of Human Enterovirus 71 Outbreaks in Sarawak, Malaysia

David Perera & Mary Jane Cardosa
Institute of Health & Community Medicine Universiti Malaysia Sarawak

The first of the large EV71 outbreaks associated with neurological disease and fatalities in the Asia Pacific was noted in Sarawak, Malaysia in 1997. This was followed by an even larger outbreak of EV71 in Chinese Taipei in 1998, and since these two critical outbreaks, EV71 has been firmly established in the region with outbreaks occurring somewhere in the region every few years.

It is thus tempting to think that these EV71 outbreaks of the past decade must be linked to the emergence of a new EV71 strain that is highly transmissible and more virulent than the strains known to have been seen occasionally in the region in the 1980s and earlier. The Sarawak 1997 and the Chinese Taipei 1998 outbreaks however surprising, were caused by quite different EV71 genogroups and were not phylogenetically linked. Sarawak saw genogroup B3 viruses while Taiwan saw genogroup C2 viruses. The genogroup B virus has steadily evolved and new genogroup B viruses have been circulating in the region (Chinese Taipei, Singapore, Japan), leading to a large EV71 outbreak occurring simultaneously in many countries in 2000 all with genogroup B4 viruses being dominant.

Sarawak has seen large EV71 outbreaks every three years since 1997, all caused by genogroup B viruses which are phylogenetically linked. Thus we have had outbreaks in 1997, 2000, 2003 and 2006. This paper compares the characteristics of the viruses associated with all these outbreaks and discusses some of the implications of these findings.

Dr. Sue Huang

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Department: National Poliovirus and Enterovirus Reference Laboratory
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National Centre for Biosecurity and Infectious Disease
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Educational Background

- September 1990-June, 1995
  Ph.D. in Molecular & Cellular Biology
  Department of Biology, University of Pennsylvania, Philadelphia, PA, USA
  Research: Development of Herpes Simplex Virus type-1 as a gene transfer vector for human neurological disease gene therapy.
- September 1985 - September 1988
  M.Sc. in Molecular Genetics, Institute of Basic Medical Sciences,
  Chinese Military Academy of Medical Sciences, Beijing, China
  Research: Expression of Hepatitis B surface antigen in mammalian cells for potential vaccine and diagnostic uses.
- September 1981 - September 1985
  B.Sc. in Neurophysiology
  Department of Biology, Nanjing University, Nanjing, China
  Research: Observations on the behavior and enkephalin content of cerebral cortex in mice after long exposure to noise.

Professional Career

May 1998-present

- Science Leader – Virology
- Head, Clinical Virology Reference Laboratories
- Institute of Environmental Science and Research
- National Centre for Biosecurity and Infectious Disease
- Wallaceville, Upper Hutt, New Zealand
- My responsibility: in charge of the WHO National Influenza Centre, WHO National Poliovirus Reference Laboratory, WHO National SARS Reference Laboratory, National Reference Laboratory for Enteroviruses and Adenoviruses,

Arbovirus Reference Laboratory, local diagnostic virology laboratory for the Wellington region and lower part of North Island.

June 1995-March 1998

- Staff scientist, Entomology Group, AgResearch Wallaceville, Upper Hutt, NZ
- Research: Cloning and expression of the ecdysteroid receptor from the Australian sheep blowfly (*Lucilia cuprina*) and its signal transduction pathway.

Publications

- *Judith* E. Mueller, Maël Bessaud, **Q. Sue Huang**, Laura C. Martinez, Patricia A. Barril, Viviane Morel, Jean Balant, Judy Bocacao, Joanne Hewitt, Brad D. Gessner, Francis Delpeyroux, Silvia V. Nates **2009** Environmental poliovirus surveillance during OPV and IPV use in Córdoba Province, Argentina. Accepted by the Journal: Applied and Environmental Microbiology
- **Q. Sue Huang**, Liza Lopez, Lisa McCallum, Bruce Adlam. **2008** Influenza surveillance and immunisation in New Zealand, 1997-2006. *Influenza and Other Respiratory Viruses 2(4):139-145*
- **Q. Sue Huang,** Liza Lopez, Bruce Adlam. **2007** Influenza Surveillance in New Zealand in 2005. *New Zealand Medical Journal 120(1256):U2851*
- James W. Matheson, Fenella J. Rich, Catherine Cohet, Keith Grimwood, **Q. Sue Huang**, David Penny, Michael D. Hendy, and Joanna R. Kirman **2006** Distinct Patterns of Evolution Between Respiratory Syncytial Virus Subgroups A and B From New Zealand Isolates Collected Over Thirty-Seven Years. *Journal of Medical Virology 2006;78:1354-1364*
- Keith Grimwood**, Q. Sue Huang,** Catherine Cohet et al **2006** Rotavirus hospitalisation in New Zealand children under 3 years of age. *Journal of Paediatrics and Child Health 42(2006) 196-203.*
- **Q. Sue Huang,** Gail Greening, Michael Baker, Keith Grimwood, Joanne Hewitt, Debbie Hulston, Lisa van Duin, Amanda Fitzsimons, Nick Garrett, David Graham, Diana Lennon, Hiroyuki Shimizu, Tatsuo Miyamura, Mark Pallansch. **2005** Persistence of oral polio vaccine virus after its removal from the immunisation schedule in New Zealand. *Lancet 366:394-96*

Enterovirus Surveillance in New Zealand

Sue Huang
National Poliovirus and Enterovirus Reference Laboratory, Institute of Environmental Science and Research, National Centre for Biosecurity and Infectious Disease,

Enteroviruses are common human viruses associated with various diseases ranging from minor febrile illness to severe, potentially fatal conditions such as aseptic meningitis, myocarditis, neonatal enteroviral sepsis and acute flaccid paralysis.

The New Zealand Enterovirus Surveillance is a voluntary and passive surveillance system to monitor trends in circulating enteroviruses and provide early warning in assisting public health interventions. It operates all year around and is based on reports from routine diagnostic services for patients attending hospitals or family doctors. All enterovirus detections and serotyping results are reported weekly, quarterly and annually by the National Poliovirus and Enterovirus Reference Laboratory at ESR. Untyped or untypable enteroviruses from hospital laboratories are referred to ESR for identification.

In this presentation, the data accumulated during 1985-2008 will be discussed. A selective group of serotypes such as E33, E13, EV71 and associated disease burden will be discussed in details.

Ms. Ding-Ping Liu

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Economy: Chinese Taipei
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Educational Background

- M.S.: Graduate School of Microbiology, Institute of Medicine, National Taiwan University
- B.S.: Department of Medical Technology, National Yang-Ming Medical College

Professional Career

- Director, Vaccine Center, Centers for Disease Control, Chinese Taipei.
- Acting Director, Division of Emerging Infectious Diseases, Centers for Disease Control, Chinese Taipei.
- Deputy Director, Division of Planning; Division of Immunization; Division of AIDS & EID, Centers for Disease Control, Chinese Taipei.

Session II: Outbreak Response

Moderator:

Dr. Ho-Sheng Wu, Director, Research and Diagnostic Center, Centers for Diseases Control, Chinese Taipei

Dr. Hiroyuki Shimizu, Chief, Department of Virology II, Global Specialized Polio Laboratory, National Institute of Infectious Diseases, Tokyo, Japan

Speaker：

Dr. Dong-Lou Xiao, Deputy-Director General, Bureau of Disease Control and Prevention, Ministry of Health, China

Dr. Tzou-Yien Lin, Superintendent, Department of Pediatrics, Chang Gung Children's Hospital, Chinese Taipei

Dr. Wanna Hanshaoworakul, Medical Epidemiologist, Department of Disease Control, Bureau of Epidemiology, Ministry of Public Health, Thailand

Dr. Nguyen Thi Minh Phuong, Head, Public Health Department, Pasteur Institute, Ho Chi Minh City, Vietnam

Dr. Ho-Sheng Wu

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Educational Background

- Ph.D. in Molecular Biology, Graduate Institute of Life Sciences, National Defense Medical Center, National Defense University.
- M.S. in Clinical Virology, Center for Advanced Medical Technology, San Francisco State University, USA.
- B.S. in Medical Technology, School of Medical Technology, Taipei Medical College.

Professional Career

- Director, Division of Surveillance and Investigation, CDC, Chinese Taipei.
- Director, Second Branch Office, CDC, Chinese Taipei.
- Director of Taipei Quarantine Station, National Quarantine Service (NQS), Chinese Taipei.

Publications

- Huang YPin, Lin TL, Kuo CY, Lin MW, Yao CY, Liao HW, Hsu LC, Yang CF, Yang JY, Chen PJ, Wu HS. (2008)The circulation of subgenogroups B5 andC5 of enterovirus 71 in Taiwan from 2006 to 2007.Virus Research 137: 206–12.
- Jian JW, Chen GW, Lai CT, Hsu LC , Chen PJ, Kuo HS, Wu HS*, Shih SR* (2008) Genetic and Epidemiological Analysis of Influenza Virus Epidemics in Taiwan during 2003 to 2006. J Clin Microbiol 46(4):1426-34.
- Lin JH, Chiu SC, Lee CH, Su YJ, Tsai HC, Peng YT, Wu HS. (2008) Genetic and antigenic analysis of epidemic influenza viruses isolated during 2006-2007 season in Taiwan. J Med Virol. 80(2):316-22.
- Lin JH, Tseng CP, Chen YJ, Lin CY, Chang SS, Wu HS, and Cheng JC (2008) Rapid differentiation of influenza A virus subtypes and genetic screening for virus variants by high-resolution melting analysis. J Clin Microbiol. 46(3):1090-7.
- Jian JW, Lai CT, Kuo CY, Kuo SH, Hsu LC, Chen PJ, Wu HS*, Liu MT.(2007) Genetic analysis and evaluation of the reassortment of influenza B viruses isolated in Taiwan during the 2004-2005 and 2006-2007 epidemics. Virus Res. 131(2):243-9

Dr. Hiroyuki Shimizu

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Educational Background

- 1980-1984: Bachelor degree from Faculty of Pharmacy, Chiba University, Japan
- 1993: Ph.D. from Faculty of Pharmacy, Chiba University, Japan

Professional Career

- 1984-1995: Research Center of Laboratory, Meiji Pharmaceutical Co. Ltd., Yokohama.
- 1995-present: Department of Virology II. National Institute of Infectious Diseases.

Publications

- Thorley B, Kelly H, Nishimura Y, Yoon YK, Brussen KA, Roberts J, Shimizu H: Oral poliovirus vaccine type 3 from a patient with transverse myelitis is neurovirulent in a transgenic mouse model. J Clin Virol 44: 268-71, 2009.
- Mizuta K, Aoki Y, Suto A, Ootani K, Katsushima N, Itagaki T, Ohmi A, M. O, Nishimura H, Matsuzaki Y, Hongo S, Sugawara K, Shimizu H, Ahiko T: Cross antigenicity among EV71 strains from different genogroups isolated in Yamagata, Japan, between 1990 and 2007. Vaccine (in press).
- Hamaguchi T, Fujisawa H, Sakai K, Okino S, Kurosaki N, Nishimura Y, Shimizu H, Yamada M: Acute Encephalitis Caused by Infrafamilial Transmission of Enterovirus 71 in Adult. Emerg Infect Dis 14: 828-830, 2008.
- Arita M, Wakita T, Shimizu H: Characterization of pharmacologically active compounds that inhibit poliovirus and enterovirus 71 infectivity. J Gen virol 89: 2518-30, 2008.
- Arita M. Ami Y, Wakita T, Shimizu H: Cooperative effect of the attenuation determinants derived from poliovirus sabin 1 strain is essential for attenuation of enterovirus 71 in the NOD/SCID mouse infection model. J Virol 82: 1787-97, 2008.

Dr. Dong-Lou Xiao

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Educational Background

- 1972-1975 Undergraduate, Shanghai Medical University
- 1979-1982 Postgraduate, Peking Union Medical College and CAMS
- 1984-1985 Visiting Scholar ,Centers for Disease Control, U.S.A ,
- 1997-1998 Visiting Scholar , Department of Molecular Microbiology & Immunology, School of Medicine, University of Missouri-Columbia Columbia, MO 65203, U.S.A
- Jan 19-24,1987 Workshop on Diarrhoeal Disease Control, WPRO,WHO ,held in Manila, Philippines
- Oct 1-25,1990 Training Course on Diagnostic Techniques and Control for Diarrhoeal Diseases, Sponsored by Research Institute for Tropical Medicine, Manila, Funded by JICA(Japan)
- Sep 5-23,1993 Training Course on Lab Diagnosis of Diarrhoeal Disease Agents, Sponsored by International Center for Diarrhoeal Disease Research(ICDDR), Bangladesh, Funded by WHO
- Dec 8-16, 1995 Workshop on Diarrhoeal Disease Control, Sponsored by WHO, Held in Laos
- July 20-31,2001 Conference on Biological Weapon Control(BMC), Geneva
- Sep 26-28 ,2001 Tokyo Influenza Surveillance Workshop , Sponsored by WPRO, WHO, held in Tokyo, Japan
- Dec 5-8,2001 Accelerating the Development and Introduction of a Dengue Vaccine for Poor Children, Ho-zhi-Mihn City, Vietnam, Sponsored by International Vaccine Institute, Seoul, Korea
- Jan 28-30,2002 Network of Networks Meeting, Sponsored by University of Washington, U.S.A
- May 6-7,2002 WHO Temporary Advisor, Global Agenda on Influenza Surveillance and Control, WHO Headquarter ,Geneva

Professional Career

- 2002-present Deputy Director-general, Dept. of Disease Control, MOH
- 2001-2002 Director, Division 1, Dept.of Disease Control, MOH
- 1999-2000 Senior Coordinator, National Center for Health Inspection, MOH
- 1995-1997 Director , Professor , Institute of Epidemiology and Microbiology, Chinese Academy of Preventive Medicine high school (IEM,CAPM)
- 1992-1994 Deputy Director, Associate Professor, IEM,CAPM
- 1988-1991 Director, Office of Scientific Research, IEM,CAPM
- 1985-1987 Chief, Department of Diarrhoeal Diseases ,IEM
- 1980-1985 Assistant Professor , IEM, CAPM
- 1975-1979 Assistant Researcher, IEM, Chinese Academy of Medical Sciences (CAMS).

Publications

- 1995-1997 Study on Immunochemistry and Immunogenicity of Outer-membrane Proteins of 01 and 0139 V. cholerae, Funded by National Foundation of Natural Sciences of China
- 1986-1987 Study on Molecular-Biological Characterization of139V.cholerae, Funded by Ministry of Health of China
- 1992-1995 Identification and Genetic Analysis of Common Diarroeal Pathogens, CDD Programme, Funded by WHO
- 1988-1991 Survival Mechanism of V.cholerae during Non- Epidemic Period, Funded by National Foundation of Natural Sciences of China
- 1986-1987 Survey on Aetiology and Epidemiology of Yersinia enterocolitica Funded by Ministry of Health of China
- 1984-1985 Study on Special Pathogens : Mycoses and Listeriosis at Centers for Disease Control, Atlanta ,GA
- 1979-1982 Study on Immunochemistry and Immunogenicity of Lipo-polysaccharide and Proteins of Brucella, as a Dissertation of Postgraduate

Strategy of Prevention and Control for HFMD in China

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1. Epidemic situation of HFMD in 2008

Totally, 489073 HFMD cases were reported in 2008 in China Mainland, with the incidence rate of 37.01/100,000. There were 1165 severe cases accounted for 0.24 % of cases reported, and 126 death with case fatality rate of 0.26‰.

All provinces in China mainland reported HFMD cases. Children under 5 years old accounted for 91.17% of reported HFMD cases, primarily affecting children under 3 years old (up to 71.66% of all cases). Children living dispersedly accounted for 66.41% of all cases, and the children in childcare centers accounted for 28.12%. 6966 lab–confirmed cases were reported, and EV71 and Coxsackie A16, separately accounted for 61.43% and 16.25%. The EV71 positive proportion of death cases, severe case and common case, separately is 96.25%, 81.79% and 60.25%.

2. Analysis of HFMD During Jan~ April of 2009

From January 1 to April 8, 2009, 122469 HFMD cases were reported (including 858 severe cases), the number of deaths reached 52. Children under 5 years old accounted for 94.5%. EV71 positive cases accounted for 58.3% of lab-confirmed cases.

The Characteristics of HFMD prevailing in China mainland are as followed. (1) HFMD Prevails in the rural area, with the trait of distributing broadly, higher proportion of infants, lasting longer time. (2) The epidemic situation is ahead of schedule relatively to former years, and shows two focus areas, one of which is the boundary area among Shandong Province, Henan province, Anhui province, Jiangsu province and expands forth, the other of which is the local hot areas of Guangdong , Guangxi and Yunnan province. Excepting Xizang, all provinces report HFMD cases. (3) The EV71 positive proportion of lab-confirmed cases is higher than that in last year, especially in Heze city, Shandong province and Minquan county, Shangqiu city, Henan province. (4) The statistic data shows the HFMD occurred in China mainland is at rising stage, the number of cases reported weekly will increase with time, and climb to the peak during May and July.

3. The strategy of Prevention and control of HFMD in China

The Government of China has shown its strong technical and political

commitment to control the HFMD in China.

3.1 Standardizing the prevention and control of HFMD as the relative regulation.

HFMD became notifiable on May 2, 2008, categorizing as a Class "C" notifiable disease. China strengthened the surveillance, report and treatment work of HFMD.

3.2 Enhancing the surveillance and analysis work to scientifically estimate the epidemic situation.

To further improve the report quality and forbid disguising the truth, the HFMD report work was standardized and strengthened. The HFMD virus surveillance was developed as plan, organizing the experts to discuss the trend of HFMD situation. Once the situation shows the sign of outbreak, the counterplan will be started to respond the outbreak. In some focus areas, “liability by individual officials” system for children under 5 years old was carried out to promote the early detection of HFMD case.

3.3 *Improving the capacity of treatment and minimization of case fatalities.*

The experts were organized to continually collect the experience of the treatment for severe cases, optimization of patient treatment manual and distributing to all hospitals. The local government standardized the patients conveying system, expert consultation and designating system. Specialized medical teams were formed and stationed at the focus area, guiding the technical training and improvement of health-care workers' professional skills. The grade-based liability treatment system was established, designating of specific hospitals for the treatment of HFMD severe patients. Meanwhile, paediatric Intensive Care Unit (ICU) facilities were established or expanded to minimize the case fatalities as possible.

3.4 *Strengthening of patient triage system and control of nosocomial infections.*

To prevent cross-transmission among the sick children, all grade hospitals established the fever and rash patient triage system. The medical service quality management and nosocomial infection control work was strengthened, as emphasizing on the patient isolation treatment to avoid HFMD spreading.

3.5 Improving the capacity of lab examination.

With professional person introducing and technical training, the lab equipment investment increased continually, and good-armed labs were formed. All Province level and partial city level CDC have the capacity of testing the HFMD samples.

3.6 Optimization the reimbursement system to assure that the HFMD patients get timely medical treatment.

The central government increased the economic investment for the HFMD focus area, and provided the control and treatment subsidy. The local governments arranged the HFMD fund, purchasing the equipment and medicine, and reimbursing the HFMD medical fees based on the new rural cooperative medical care regulation. These

measures greatly relieve the economic burden of the HFMD cases families.

3.7 Starting full scale health campaign, promulgating the knowledge of HFMD prevention and control.

Full scale health campaign was started to improve the environment health, including food safety, water safety and public place health safety, with focus on childcare centers and schools. Prevention and control measures for HFMD are being promoted through various channels, promulgating the knowledge of HFMD prevention and control, advocating healthy sanitation practice to motive all people participating the HFMD prevention and control work.

3.8 Strengthening the risk communication, timely and accurately disseminating the information.

Risk communication was carried out, actively, timely, accurately and objectively disseminating the HFMD information to get the initiative of news and maintain society stabilization. The cooperation with medium was further strengthened, such as broadcast, TV, to disseminate the infectious disease (such as HFMD) information regularly or at any time needed. Information on HFMD in China mainland was also timely reported to WHO and exchanged with Hong Kong, Macau and Taiwan .

3.9 Fully exerting the role of research work.

China government rapidly organized the research teams to promote the detecting reagent and vaccination research work, guiding local government to do some base research work. The experts of some province-level CDC were trained to accomplish the virus isolation and population serological epidemiology research, providing the scientific data for the HFMD prevention and control.

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Epidemiology of Enterovirus 71 in Chinese Taipei, with an Introduction of Modeling System

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In 1998, a large outbreak of enterovirus 71(EV71) occurred in Chinese Taipei. There were 405 severe cases with 78 deaths. 90% of severe cases occurred in children younger than 4 years old. Most children with EV71 infection presented with hand footand mouth disease initially. Around 20% of hospitalized patients progressed to CNS involvement but only a few of them further advanced to cardiopulmonary failure.

Since then, EV71 infection became endemic in Chinese Taipei. The outbreak occurred in Chinese Taipei each year. After decreased EV71 activities in 2006 and 2007, with resultant accumulation of susceptible population, a big outbreak took place in 2008. There were 373 severe cases and 14 deaths.

Currently, there are four surveillance systems for enteroviral activity in Chinese Taipei: 1) Sentinel physician system to monitor hand foot and mouth disease and herpangina. 2) National notifiable diseases surveillance to monitor severe cases. 3) Contracted-laboratory based virological surveillance system to monitor viral activities. 4) Realtime outbreak & disease surveillance system (RODS). Since 2008, electronic system for report and review severe diseases was implemented.

To identify transmission dynamics and to estimate the potential number of severe EV71 cases, a mathematical modeling is developing. We used 1999-2003 epidemic data for modeling training and curve fitting, and 2004-2008 data for modeling testing and parameter validation. Results estimated an average of 56±33 severe EV71 cases will be identified between March & October of 2009. The modeling also suggests that March & April be the key timing to predict the scale of an EV71 outbreak.

With the development of stage-based management, the mortality rate decreased from 19 % in 1998 to 15 % in 2001, and 3.8 % in 2008. But the neurological sequelae have increased. Vaccination is the only way to control EV71 outbreak. A cohort study in Chinese Taipei showed that seropositive rate of EV 71 in pregnant women was 65%,

in neonates was 50%, and the rate decreased to 1.2% in infants age 6 months. This study suggested that the target age for inactivated EV71 immunization would be infants younger than 6 months of age.

Phylogenetic analysis of EV71 suggested possible importation & exportation in Asia-Pacific region. Regional cooperative system for EV71 surveillance, standardized viral identification and management is mandatory.

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HFMD Situation and Control in Thailand

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Hand Foot and Mouth Disease (HFMD) was concerned as a public health problem in Thailand after outbreaks of Enterovirus71 during 1997-2000 in several countries. Since 2001, all health care facilities were motivated to report HFMD cases to the public health authorities under the surveillance system. The admitted cases and cluster of cases should be investigated to identify the causative agent. Incidence of HFMD cases gradually increased during 2001-2006 and markedly increased during 2005-2007. The incidence cases in 2005-2007 were 7.47, 6.33 and 26.81 per 100000 populations respectively. There is no seasonality pattern observed. The cases are reported from every province. Eighty five percent of cases are children less than 5 years. There was sporadic 0-2 deaths reported annually since 2001 except in 2006 there were 7 deaths. The investigation of 7 deaths found pulmonary edema (100%), leukocytosis (100%), and hyperglycemia (71%). The median age was 11 months (7-19 months). EV71 was isolated from 3 of 7 deaths.

The control measures involve health care facilities and child care institute. Hand hygiene and good sanitation are recommended during normal period. The outbreak containment measures including 1) If two or more cases in the same class room, consider closing the class room, 2) If there are two or more class rooms are affected, consider closing the school/institute. Hands hygiene, cleaning and close observation for case detection and isolation should be continued until the outbreak subsided. Although the recommendations are simple and clear, there is no scientific evidence to ensure the effectiveness of those activities.

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- Mass psychogenic illness following oral cholera immunization in Ca Mau City, Vietnam.
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- Evaluation the impact of measles mass campaign for children from 9 months to 10 year in the Southenr region, 2003 .

Hand Foot Mouth Disease Surveillance
In The Southern Region of Vietnam from 2005-2008

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Hand foot mouth disease is increasing remarkably and causes bad influence on Human health, especially on the children health in three years from 2005 to 2007 at Children's hospital number 1 in Ho Chi Minh City, south of Viet Nam. The numbers of children were hospitalized and confirmed hand foot mouth disease is increasing from 441 to 2,284 and 2,988 children, including 95 - 432 - 1,348 cases having the complication on nervous system and 13 - 13 - 14 cases were died. Finally, in 04 months of 2008, the morbidity reaches 67.4% the morbidity of the year 2007 with 2,015 infected cases, 435 cases having the complication on nervous system and 06 cases were died.

However, the surveillance for this disease has not been performing officially and well in the southern region before 2008. The statistics and report on morbidity and mortality mainly come from hospitals in Ho Chi Minh City. Based on the consequences of the increasing cases dramatically and the serious of hand foot mouth disease, the MOH of Viet Nam has established the hand food mouth disease surveillance in whole country since May 2008 with the integration into the 26 notifiable diseases. Otherwise, the quality of information from this surveillance system still has not been guarantied: the statistic, report and feedback have not perform exactly, in fact that the 26 notifiable diseases only records aggregate data, lack of information on demography, epidemiology and testing results, the outbreak response has got a lot of difficulties in responding to the outbreak sufficiently and efficiently.

Regarding all the reasons above, establishing the concrete surveillance and response system to the hand foot mouth disease is very fundamental in order to predict the emergence of outbreak and implement the outbreak response in time and effectively in the southern region of Viet Nam.

Session III Clinical Diagnosis & Treatment

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Early Recognition and Management of Complicated Hand, Foot, and Mouth Disease: The Sarawak Experience

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Hand, foot, and mouth disease (HFMD) is a common febrile rash illness among children, most commonly caused by coxsackievirus A16 and human enterovirus 71 (HEV71). In most instances the childhood exanthema particularly that due to coxsackievirus A16 is a benign self-limiting illness. However, since 1997 the normally considered innocuous childhood exanthema has become a growing regional public health problem following frequent epidemics of death-associated HFMD due to HEV71 in Sarawak, Malaysia and many other countries across Asia. A total of 20 deaths occurred in Sibu Hospital during the first ever documented HEV71-associated HFMD epidemic in Sarawak in 1997. Fatal cases typically presented with a short duration of febrile illness, subtle neurological signs and died unexpectedly of fulminant cardiac dysfunction and pulmonary oedema within hours of developing signs of cardiorespiratory distress. Late diagnosis and late intervention were important contributing factors to the alarming number of fatalities. Cerebrospinal fluid (CSF) pleocytosis has been the universal finding in almost all the fatal cases even though many have no obvious neurological signs prior to the onset of cardiorespiratory failure.

Early recognition and timely intervention in children at risk of neurological involvement and cardiorespiratory failure is the key to reduce acute mortality and morbidity. In Sarawak the effort is often hindered by acute shortage of doctors particularly in the rural areas, where paramedics are the principal primary care providers. This is compounded by the challenging geographical terrains that frequently limit the patients' accessibility to healthcare facilities and medical attention. Our data showed that history of lethargy, mean peak temperature ≥38.5°C and duration of fever ≥3 days were three independent risk factors predictive of CNS involvement. Screening for these readily elicited risk factors may be performed by paramedics with minimal training, and has formed an integral part of HFMD patient triage at the primary care centers in Sarawak. After the 1997 epidemic our management approach has been geared toward early diagnosis and timely intervention

in children at risk of cardiorespiratory failure (particularly those with encephalitis and encephalomyelitis). Children with suspected CNS involvement are investigated with CSF examination. Intravenous immunoglobulin infusion is considered in children who have CSF pleocytosis, particularly in those with high fever, tachycardia, tachypnea and myoclonus. Our data showed that this approach has reduced the mortality rate in children who had severe and potentially fatal CNS complications seen in subsequent HEV71 epidemics between 2000 and 2006 (204 [95%] of 215 cases that survived had timely hospital admission and intravenous immunoglobulin treatment compared to 1 (11%) of 9 cases that died (OR 148.36, 95%CI 16.34–6609.04, $p < 0.0001$).

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Clinical Manifestations, Diagnosis and Long-term Outcome of EV71

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The enterovrius 71 (EV71) outbreak in Chinese Taipei in 1998 is very well-known to cause a lot of fatal children cases. In 1998 epidemic, there were 405 severe cases with 78 deaths. In 2000 to 2002, there were still dozens of fatal EV71 cases each year. According to our clinical studies, symptomatic enterovirus 71 (EV71) infection can progress through four stages: HFMD/herpangina (Stage 1), CNS involvement (Stage 2), cardiopulmonary failure (Stage 3), and convalescence (Stage 4). Most EV71 cases in those studies stayed at stage 1, some progressed to Stage 2 and a few would advance to the most severe condition, Stage 3.

A stage-based management was thus developed to reduce the case-fatality but most survivors of brainstem encephalitis plus cardiopulmonary failure might have neurologic sequelae and impaired cognition. Nine (56%) of the 16 polio-like cases and 1 (20%) of the 5 encephalomyelitis cases had sequelae involving limb weakness/atrophy. Eighteen (64%) of the 28 cases with cardiopulmonary failure after CNS involvement had limb weakness and atrophy, 17 (61%) required tube feeding, and 16 (57%) required ventilator support. Delayed neurodevelopment was found in only 1 (5%) case with severe EV71 CNS involvement and in 21 (75%) cases with cardiopulmonary failure ($p<0.001$). Children with cardiopulmonary failure after CNS involvement scored lower on intelligence tests than children with CNS involvement alone ($p=0.003$). Among patients with CNS involvement alone, children infected at ages younger than 2 had lower verbal comprehension than children infected at older ages ($p=0.009$).

EV71 CNS involvement with cardiopulmonary failure may be associated with neurological sequelae, delayed neurodevelopment and reduced cognitive functioning. Children with CNS involvement without cardiopulmonary failure did well in neurodevelopment. Continuous EV71 disease and laboratory surveillance is warranted to allow for possible earlier control and prevention measures.

Key words: EV71, manifestations, outcome, sequelae, cognition

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- Shih-Min Wang, Huan-Yao Lei, Chun-Keung Yu, Jen-Ren Wang, Ih-Jen Su, Ching-Chuan Liu*. Acute chemokine response in the blood and cerebrospinal fluid of children with enterovirus 71 brainstem encephalitis. J Infect Dis 2008198:1002-6. (Corresponding author)

Pathogenesis-based Management of Enterovirus 71 Brainstem Encephalitis

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Several epidemic outbreaks of enterovirus infection occurred during the past one decade in Formosa. Enterovirus 71 (EV71) has the potential to cause a large outbreak worldwide such as that in Formosa in 1998. The main clinical presentations were hand-foot-and-mouth disease (HFMD), herpangina, and central nervous system (CNS) involvement. Brain stem encephalitis (BE) was the cardinal feature of EV71 CNS involvement during the outbreak. BE that progressed abruptly to neurogenic shock and pulmonary edema (PE) was indicative of poor prognosis. EV71 BE was categorized into uncomplicated BE, autonomic nervous system (ANS) dysregulation, and PE by disease severity. The PE that occurs in children with EV71 BE is caused by abnormal cytokines activation that produces severe CNS and systemic inflammatory responses. We found a decrease in the plasma concentration of various cytokines following administration of intravenous immunoglobulin (IVIG). Patients with ANS dsyregulation is the critical timing to received IVIG infusion. It is possible that a more favorable survival might have been obtained by earlier therapy and larger doses of IVIG. Early treatment with milrinone (Primacor®) among patients with EV71-induced PE decreased autonomic activity, reduced white blood cell counts, platelet counts, and plasma levels of IL-13, and significantly decreased mortality. Controlled clinical trials are needed to confirm these observations. A better understanding of the clinical features and management of EV71 BE may shed light on improving the outcome of severe and complicated EV71 BE.

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Educational Background

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- 2001 - 2003 Master of science, Ha Noi Medical University Expert on: Pediatrics - Infectious diseases

Professional Career

- 1996-2009-13 years working in infectious diseases dept in NHP Ha noi, Vietnam as pediatrician.
- 2002-2009-8 years of take care children with HIV/AIDS in NHP

Publications

- Clinical manifestations, epidemiology by etiology of bacterial meningitis in children. Year book of Vietnam Pediatrics scientific conference 17th-2000. Hanoi, Vietnam
- Assessment of clinical manifestations and laboratory finding by etiology on prolong fever patients in national hospital of pediatric. Journal of Medical research – Hanoi Medical University. Supplement. Vol 38, No5., Nov-2005.
- Clinical manifestations, laboratory findings, some risk factors of HIV infected children among inpatients in NHP from 9/2004-9/2005. Journal of Medical research – Hanoi Medical University. Supplement. Vol 38, No5., Nov-2005.
- Study of clinical, paraclinical characteristics in HIV/AIDS children treated by anti-retroviral drug at NHP in 2007. Journal of military pharmaco-medicine. Vol 33, No8/2008

Enteroviral Encephalitis in Vietnam National Hospital of Pediatrics: Epidemiology, Clinical Manifestations, Laboratory Findings and Outcome

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Background:
Viral neurological infections are common and can be very severe. Viral encephalitis causes include: JE, HSV1, Enterovirus, Mumps, Measles, Influenza & Varicella. Since a national immunization program for Japanese Encephalitis was introduced in 2005, non-polio Enterovirus has become more common.

Aims of the study:
To describe the epidemiology, clinical manifestations, laboratory findings, and outcomes of enterovirus encephalitis who were treated at the National Hospital of Pediatrics in Hanoi in 2006.

Study design:
Case series.

Results and Conclusion:
33 patients with diagnosis EV encephalitis: 25 boys (75%) and 8 girls (25%). Most common in young children, particularly the child under 3 years old (42%). The disease was found throughout the year and predominant in March. High fever, seizure, coma and anemia were most common clinical signs and symptoms. WBC in CSF elevated not over 100cell/mm3. Multiple lesion on CT-Scan film. Complete recovery (70%), sequel (15%), death (15%).

Key words: Enteroviral Encephalitis

Session IV: New Technology & Biotech Industry

Moderator：

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Dr. Hong-Jen Chang, Advisor, Centers for Diseases Control, Chinese Taipei

Speaker：

Dr. Joseph D Santangelo, CEO, SingVax Pte Ltd., Singapore

Dr. Pele Choi-Sing Chong, Distinguished Investigator & Director, Vaccine and Development Center, National Health Research Institutes, Chinese Taipei

Prof. Yu-Chen Hu, Professor, Department of Chemical Engineering, National Tsing Hua University, Chinese Taipei

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Educational Background

Elementary Education: University of Nueva Caceres, Naga City, 1963 2nd Honors
High School Education: University of Nueva Caceres, Naga City, 1967 1st Honors
College Education: University of the Philippines, Diliman, 1971

Honors and Scholarships:

Entrance Scholar, 1967
College Scholar, 1969
UP – PNB Scholar, 1969-1971
Member, UP Pre-med Honor Society, 1967 – 1971
Member, Pi Gamma Mu Honor Society, 1971
Member, Phi Kappa Phi International Honor Society, 1971

Medical Education: University of the Philippines, 1975

Honors and Awards:

Entrance Scholar, 1971
10 Most Outstanding Clinical Clerk in Pediatrics

Internship: Philippine General Hospital, 1976

Award:

10 Most Outstanding Intern in Ophthalmology

Passed: Physicians Board Examination, Complete, 1976 Rating 88.3

Postgraduate Training and Employment: General Medicine:

- Rural Service Program, Department of Health, Rural Health Unit, Pili, Camarines Sur, 1976 to 1977
- Instructor IV, Department of Physiology, University of the Philippines College of Medicine, 1977 to 1978
- Medical Officer, Casualty Unit, Lagos General Hospital, Lagos, Nigeria, 1978 to 1979
- Resource Person, Christoffel Blinden Mission-sponsored Seminars on Prevention of Blindness: Davao City and Midsayap, North Cotabato, 1984-1985
- Consultant, Flying Medical Samaritans – Sponsored Medical Missions in Sulu

and Zamboanga, 1986 – 1988

- Consultant, Medical Mission in Lagawe, Ifugao, 1968
- Chief Medical Officer, Christian Medical Specialists Care Foundation, 1989-1990

Residency in Ophthalmology:

Philippine General Hospital, 1981 – 1983

Papers Written:

- *Cimetidine: A Histamine H2 Receptor Antogonist and its Use in Ophthalmology*, A Literature Review, Annual Report, Volume 2, Department of Ophthalmology, UP-PGH 1981
- Acupuncture Anesthesia in Ophthalmology, A Literature Review, Annual Report, Volume 2, Department of Ophthalmology, UP-PGH, 1982
- *Phthyriasis Pubis Palpebrarum in a Family*, A case Report, Unpublished, 1983
- *Bilateral Optic Nerve Drusens*, A case Report, Unpublished, 1983
- *Retinal Nematode Cyst,* A Case Report, Unpublished, 1983
- *Comparative Psychophysical Evaluation Between Acupuncture Analgesia* and *Topical Anesthesia on Corneas of Filipinos*, Philippine Journal of Ophthalmology, 1994

Postgraduate Training: General Ophthalmology

- Kiryu Eye Institute, Gunma, Japan, 1988, Dr. Akira Momose
- Prince Charles Eye Unit, King Edward VII Hospital, Windsor, England, 1989, Mr. Jack Kanski

Postgraduate Training: Pediatric Ophthalmology and Strabismus

- Royal Berkshire Hospital, Reading, England, 1992, Mr. A. B. Richards
- Hospitals for Sick Children, London, England, 1992, Dr. David Taylor

Seminars and Workshops Attended: International

- 1st International Cataract, Implant, Microsurgical and Refractive Keratoplasty Meeting, June 13-15, 1987, Singapore
- 2nd International Cataract, Implant, Microsurgical and Refractive Keratoplasty Meeting, July 1-3, 1988, Nagoya, Japan
- Workshop on Radial Keratoplasty by Dr. Fyodorov, July 8-10, 1988, Gunma,

Japan

- International Strabismus Association Convention, 1995, Kyoto, Japan
- International Strabismus Association Convention, 2000, Stockholm, Sweden
- Southeast Asia Glaucoma Interest Group, October, 2002, Manila Philippines

- International Conference on Myopia, November, 2002, Hongkong and Guanzhou, China

Hospital Affiliations:

- East Avenue Medical Center, Department of Ophthalmology, Section of Pediatric Ophthalmology and Strabismus Chief, Information and Continuing Education Unit
- Eye Referral Center, TM Kalaw, Manila, Active Consultant
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- Philippine Medical Association, Quezon City Chapter, Life Member
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- Philippine Society of Pediatric Ophthalmology and Strabismus, Founding Member
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- M.D , Nation Yang-Ming Medical College

Professional Career

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- M.Sc. in Microbiology – University of Vermont (USA)
- Ph.D. in Industrial Microbiology and Genetics – University of Cape Town (South Africa)

Professional Career

Alexander von Humboldt Fellow, Univ. Goettingen (Germany); Infectious Diseases Dept, Imperial College (London, UK); Founder and Associate Director, Microscience Ltd. Founder and CEO, SingVax Pte Ltd.

Overcoming Challenges in the Development of an EV71 Vaccine

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Most if not all vaccines licensed for sale have been developed to address the needs of the most financially lucrative markets, namely the United States and Europe. Diseases of relevance to Asia have often been overlooked as vaccine targets until they become economically viable products which warrant the expensive outlay associated with biopharmaceutical product development. SingVax was founded on the principle of addressing the vaccine development needs for diseases of relevance to Asia, including the development of an EV71 Hand Foot and Mouth Disease pediatric vaccine.

The development of any vaccine or biopharmaceutical faces considerable challenges and this includes the development of an EV71 vaccine. The presentation will address a number of these challenges, from perception, market and science.

Hand Foot and Mouth Disease (HFMD) is generally benign and self limiting, thus there has been some resistance in the medical community in supporting the development of a vaccine. Parallel to this resistance is support for investment into such a vaccine, particularly in developing countries where other healthcare issues may predominate. The value of an EV71 vaccine is often questioned under these circumstances.

As with any vaccine, sound science must provide a foundation for antigen selection and demonstration of pre-clinical and clinical efficacy. There is an abundance of literature on the epidemiology of EV71 outbreaks, and this had led to classification of at least 11 different genogroups of EV71 with only one serogroup. The requirements for an effective EV71 vaccine antigen strain may not necessarily lead to the choice of a recent circulating genotype. We will discuss the genetics and immunology behind the selection of our EV71 antigen strain and provide a robust argument for our selection.

Similarly, cross protection against all EV71 isolates and also preferably against Coxsackie A16 is important for a HFMD vaccine to be efficacious. The challenge of

demonstrating cross protection is not easy to overcome. Potential problems will be discussed along with possible solutions.

Last, an update on the development of SingVax's proprietary EV71 vaccine will be presented with a focus on process development and in-vitro studies.

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Professional Career

- Distinguished Investigator and Director, Vaccine Research and Development Center, National Health Research Institutes, Chinese Taipei (2003-present)
- Vice President and Chief Scientific Officer of UBI (USA) and UBI- Asia (Chinese Taipei)(2000-2003)
- Corporate Platform Leader and Research Director at Aventis Pasteur Canada, Canada (1994-2000)
- Project Manager for HIV Synthetic Vaccine Development at Pasteur Merieux Connaught, Canada (1990-1996)
- Research Scientist, Connaught Laboratories Limited, Canada (1985-1990)
- MRC Postdoctoral Fellow at department of Pathology, University of British Columbia, Canada (1983-1985)

Publications

- Hsin-Wei Chen, Shih-Jen Liu , Hsueh-Hung Liu, Yan Kwok, Chang-Ling Lin, Li-Hsiu Lin, Mei-Yu Chen, Jy-Ping Tsai, Li-Sheng Chang, Fang-Feng Chiu, Li-wei Lai, Wei-Cheng Lian, Chiou-Ying Yang, Shih-Yang Hsieh, Pele Chong, Chih-Hsiang Leng. “A novel technology for the production of a heterologous lipoprotein immunogen in high yield has implications for the field of vaccine design”. Vaccine. 2009; 27:1400-1409.
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- Pele Chong. The Asian Vaccine Industry: Opportunities and challenges. Pharma Focus Asia. 2008; 6:42-48.

NHRI Vero Cell-based EV71 Vaccine Development

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The EV71 infections in human are commonly as a childhood exanthema known as hand-foot and-mouth disease; it could cause neurological disease during acute infection. EV71 outbreaks have created significant problems in Asia; EV71 vaccine isnow urgently needed. Based on the poliovirus vaccine development concept, the cell-based culture system is suitable in manufacturing inactivated EV71 vaccine. In the report, we will describe the Vero cell-based inactivated EV71 vaccine development currently performed in NHRI.

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Educational Background

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- 1988-1992: BS in Chemical Engineering, National Taiwan University.

Professional Career

- 2007-present: Professor, Department of Chemical Engineering, National Tsing Hua University.
- 2003-2007: Associate Professor, Department of Chemical Engineering, National Tsing Hua University.
- 2000-2003: Assistant Professor, Department of Chemical Engineering, National Tsing Hua University.
- 1999-2000: Visiting Fellow, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health.

Publications

- Chuang, C.-K., Wong, T.-H., Hwang, S.-M., Chang, Y.-H., Chen, Y.-H., Chiu, Y.-C., Huang, S.-F., Hu, Y.-C.*. Baculovirus transduction of mesenchymal stem cells: In vitro responses and in vivo immune responses after cell transplantation. Mol. Ther. In press. (SCI 5.862).
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Development of Virus-Like Particle (VLP)-Based Enterovirus-71 Vaccine

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The primary objective of this study is to develop virus like-particle (VLP)-based vaccine against EV71. We employed the baculovirus expression system to produce P1 and 3CD proteins of enterovirus 71 (EV71), by which 3CD cleaved the P1 structural protein into individual proteins, leading to the assembly of EV71 VLP. After immunization of BALB/c mice, EV71 VLP induced potent and long-lasting humoral immune responses as evidenced by the high total IgG titer and neutralization titer. The splenocytes collected from the VLP-immunized mice exhibited significant cell proliferation and produced high levels of IFN-γ, IL-2 and IL-4 after stimulation, indicating the induction of Th1 and Th2 immune responses by VLP immunization. More importantly, the VLP immunization of mother mice conferred protection (survival rate up to 89%) to neonatal mice against the lethal (1000 LD_{50}) viral challenge. Compared with the VLP immunization, immunization with denatured VLP and heat-inactivated EV71 elicited lower neutralization titers and conferred less effective protection to newborn mice, although they induced comparable levels of total IgG and cellular immune responses. Furthermore, the VLPs were purified by size-exclusion chromatography for monkey immunization, which resulted in robust induction of humoral immune responses in monkeys. These data altogether implicated the potential of EV71 VLPs as a promising vaccine candidate.

Session V: Laboratory Technology

Moderator：

Dr. Dustin Chen-Fu Yang, Microbiologist, Research and Diagnostic Center, Centers for Disease Control, Chinese Taipei

Prof. Dominic Dwyer, Professor, Department of Virology, Centre for Infectious Diseases and Microbiology, Westmead Hospital, Australia

Speaker：

Dr. Hiroyuki Shimizu, Chief, Department of Virology II, National Institute of Infectious Diseases, Tokyo, Japan

Dr. Alexander Lukashev, Lab Head, Molecular Biology, Chumakov Institute of Poliomyelitis and Viral Encephalitides, Russia

Prof. Yuh-Shyong Yang, Professor, Institute of Molecular Medicine and Bioengineering, National Chiao Tung University, National Nano Device Laboratories, Instrument Technology Research Center, Chinese Taipei

Mr. Ratigorn Guntapong, Chief, Enteric Viruses Section, Department of Medical Sciences, National Institute of Health, Thailand

Dr. Nguyen Thi Hien Thanh, Vice Head, Virology Department, National Institute of Hygiene and Epidemiology, Ha Noi, Vietnam

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Educational Background

- PhD in Microbiology, University of North Texas, Denton, 1984
- Master in Public Health, National Taiwan University, 1971
- BS in Medical Technology, National Taiwan University, 1968

Professional Career

- Microbiologist, Centers for Disease Control, Chinese Taipei, 2006 to the present.
- Microbiologist, Centers for Disease Control and Prevention, Atlanta, 1988 to 2006

Prof. Dominic Dwyer

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Educational Background

- 1978 BSc (Med) Bachelor of Science (Medicine) University of New South Wales.
- 1980 MBBS Bachelor of Medicine, Bachelor of Surgery University of New South Wales.
- 1986 FRACP Fellow of the Royal Australasian College of Physicians.
- 1992 FRCPA Fellow of the Royal College of Pathologists of Australasia.
- 2000 .MD Doctor of Medicine University of New South Wales

Professional Career

1980-1983	Intern, Resident Medical Officer and Medical Registrar St. Vincent's Hospital, Sydney.
1984-1988	Registrar in Infectious Diseases and Virology Westmead Hospital, Sydney.
Sep 1988 -Dec 1990	Stagiaire (Research Fellow) Unitè d'Oncologie Virale, Institut Pasteur, Paris, France.
Jan 1991 -Feb 1997	Staff Specialist in Infectious Diseases Centre for Infectious Diseases and Microbiology ICPMR, Westmead Hospital, Sydney.
1997-Current	Senior Medical Virologist Centre for Infectious Diseases and Microbiology Laboratory Services, ICPMR, Westmead Hospital

Publications

MacIntyre CR, Cauchemez S, Dwyer DE, Seale H, Cheung P, Browne G, Fasher M, Wood J, Gao Z, Booy R, Ferguson N. Face mask use and control of respiratory virus transmission in households. Emerging Infectious Diseases 2009; 15:233-241.van Hal SJ, Herring B, Deris Z, Wang B, Saksena NK, Dwyer DE. HIV-1 integrase polymorphisms are associated with prior antiretroviral drug exposure. Retrovirology 2009, 6:12 doi:10.1186/1742-4690-6-12.

Taylor J, McPhie K, Druce J, Birch C, Dwyer DE. Evaluation of twenty rapid antigen tests for the detection of human influenza A H5N1, H3N2, H1N1 and B viruses. Journal of Clinical Virology (in press)

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Hurt AC, Ernest J, Deng YM, Iannello P, Besselaar T, Birch C, Buchy P, Chittaganpitch M, Shu-Chun C, Dwyer DE, Guigon A, Harrower B, Kei IP, Kok T, Lin C, McPhie K, Mohd A, Olveda R, Panayoto T, Scott L, Smith D, Smith L, Rawlinson W, Komadina N, Shaw R, Kelso A, Barr IG. Emergence and spread of oseltamivir-resistant A(H1N1) influenza viruses in Oceania, South East Asia and South Africa. Antiviral Research (in press).

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Educational Background

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- 1993: Ph.D. from Faculty of Pharmacy, Chiba University, Japan

Professional Career

- 1984-1995: Research Center of Laboratory, Meiji Pharmaceutical Co. Ltd., Yokohama.
- 1995-present: Department of Virology II. National Institute of Infectious Diseases.

Publications

- Thorley B, Kelly H, Nishimura Y, Yoon YK, Brussen KA, Roberts J, Shimizu H: Oral poliovirus vaccine type 3 from a patient with transverse myelitis is neurovirulent in a transgenic mouse model. J Clin Virol 44: 268-71, 2009.
- Mizuta K, Aoki Y, Suto A, Ootani K, Katsushima N, Itagaki T, Ohmi A, M. O, Nishimura H, Matsuzaki Y, Hongo S, Sugawara K, Shimizu H, Ahiko T: Cross antigenicity among EV71 strains from different genogroups isolated in Yamagata, Japan, between 1990 and 2007. Vaccine (in press).
- Hamaguchi T, Fujisawa H, Sakai K, Okino S, Kurosaki N, Nishimura Y, Shimizu H, Yamada M: Acute Encephalitis Caused by Infrafamilial Transmission of Enterovirus 71 in Adult. Emerg Infect Dis 14: 828-830, 2008.
- Arita M, Wakita T, Shimizu H: Characterization of pharmacologically active compounds that inhibit poliovirus and enterovirus 71 infectivity. J Gen virol 89: 2518-30, 2008.
- Arita M. Ami Y, Wakita T, Shimizu H: Cooperative effect of the attenuation determinants derived from poliovirus sabin 1 strain is essential for attenuation of enterovirus 71 in the NOD/SCID mouse infection model. J Virol 82: 1787-97, 2008.

Identification of Specific Cellular Receptors for Enterovirus 71

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Enterovirus 71 (EV71) and coxsackievirus A16 (CVA16), belonging to human enterovirus species A (HEV-A), are major causative agents of hand, foot and mouth disease (HFMD) and EV71 is also associated with various neurological diseases, such as aseptic meningitis, polio-like paralysis, acute encephalitis, and fatal neurogenic pulmonary edema, mainly in young children and infants. Severe EV71 outbreaks with a number of fatal encephalitis cases have a major impact in public health, particularly in the Asia-Pacific region from the late 1990s to 2009. Among human enteroviruses (EVs), live-attenuated and inactivated poliovirus vaccines have been used to prevent poliomyelitis and to control the transmission of polioviruses (PVs), however, no antiviral agents and vaccines are available for other EVs including EV71 to date.

The identification of specific enterovirus receptors allowed us to study the early virus-host interaction and viral pathogenesis at the molecular level, particularly for PVs, using cell lines and transgenic mice, expressing human poliovirus receptor, CD155. However, the receptor for HEV-A, including EV71, has remained elusive so far. Recently we have identified human P-selectin glycoprotein ligand-1 (PSGL-1; CD162), a sialomucin membrane protein expressed on Jurkat T lymphocytes as a functional receptor for EV71 using an expression cloning method by panning (Nishimura *et al.* Nature Medicine, published online 21 June 2009). Yamayoshi *et al.* have independently identified scavenger receptor class B, member 2 (SCARB2) as another functional EV71 receptor expressed on RD cells (Nature Medicine, published online 21 June 2009). The identification of two EV71 receptors, PSGL-1 and SCARB2, sheds new light on leukocyte and nonleukocyte cells in cell tropism and pathogenesis during the course of HFMD and severe EV71-mediated diseases. The possible involvement of multiple EV71 receptors on cell tropism and pathogenesis will be discussed. The identification of EV71 receptors would be also critical to elucidate novel therapeutic targets in EV71 replication, to establish novel laboratory diagnosis methods, and to develop more reliable small animal models, for further development of antivirals and vaccine candidates.

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Educational Background

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Professional Career

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- 2002-2006 PostDoc in Finland, Turku; Switzerland, Lausanne; UK, StAndrews.
- Interests: genetics and evolution of viruses, emerging pathogens

Publications

- Recombination in Circulating Enterovirus B: independent evolution of structural and non-structural genome regions. Lukashev A.N., Lashkevich, V.A, Ivanova, O.E., Koroleva, G.A., Hinkkanen, A.E., Ilonen, J. J Gen Virol. 2005
- Role of recombination in evolution of enteroviruses. Lukashev A.N. Rev Med Virol 2005
- Late expression of the prodrug-activating enzyme nitroreductase in an oncolytic adenovirus sensitises colon cancer cells to the prodrug CB1954. Lukashev A.N., Fuerer C., Chen, M.J., Searle P., Iggo R. 2007
- Evidence of frequent recombination among human adenoviruses. Lukashev AN, Ivanova OE, Eremeeva TP, Iggo RD. J Gen Virol. 2008
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Frequent Recombination: a Keystone of Enterovirus Genetics

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Recombination has been a well known feature of poliovirus genetics; however ubiquitous recombination among non-polio enteroviruses became truly appreciated only during the last decade. Recombination apparently occurs every few years or even months in the phylogenetic history of circulating enterovirus strains. Genome fragments of enterovirus genome have different evolutionary history even on a short timescale. New enterovirus recombinant forms emerge every few months and promptly spread over the globe, however impact of recombination on virus pathogenicity is not clear. Recombination occurs predominantly in the non-structural genome region, most frequently on the edges of the P1 (capsid-encoding) genome region. At first glance, recombination seems to be a feature that promotes enterovirus diversity. A closer look shows that recombination is confined to enterovirus species and is probably the force that constrains evolution of species on a global scale and allows highly conserved non-structural genes to efficiently change capsids and in the same time prevent further speciation.

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Nanowire Field-effect Transistor for Ultrasensitive, Label-free and Real-time Detection of Enteroviruses

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Nanotechnology and modern electronics can be the solution for a variety of biomedical problems. In this report, nanowire semiconductor device is shown to be a powerful tool for molecular diagnosis. An ultrahigh sensitivity, label-free, real time detection and easy to use biosensing system using nanowire field-effect transistor has been demonstrated[1-5]. Due to its high surface ratio and low defect in a nano scale, ploy crystalline silicon nanowire field-effect transistor (PNW FET) exhibits excellent electric properties suitable for biosensing application in aqueous environment[2]. A low cost silicon method, compatible with current commercial semiconductor process, is employed for fabrication of the nano device, which is important for its future biomedical application. DNA or antibody, complementary to the targets of interest, is immobilized on the nanowire surface of PNW FET. The electronic response of PNW FET is very sensitive to the variation of charges on its surface and the high sensitive and high specificity diagnosis is achieved when the target DNA/RNA or antigen protein interacts on the nanowire surface. Avian influenza viruse DNAs, H5 and H7 subtypes, are specifically moninotred at fM range[5]. Similar results were obtained for DNA of Enterovirus type 71. A semiconductor chip analyzer system is being developed in medical center for testing clinical samples. A multidisciplinary team from National Chiao Tung University, National Nano Device Laboratories, Instrument Technology Research Center and China Medical University Hospital is working together for integrating PNW FET into an Enterovirus sensing instrument.

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- Molecular epidemiology of wild type 1 poliovirus in Thailand during 1992-1995. J infect Dis Antimicrob Agents 1997; 14:79-86.
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Molecular Epidemiology of EV71 in Thailand, 2008

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Hand Foot and Mouth disease (HFMD) is a contagious enteroviral infection occurring primarily in children and characterized by a vesicular palmoplantar eruption and erosive stomatitis. Patient's specimens were sent to the National Institute of Health, Department of Medical Sciences, Nonthaburi during January and December, 2008 for viral isolation. Total of 1,129 specimens from 921 cases were notified with 5 deaths. From all cases, 18.6 % of children with HFMD were age below 4 years. 204 of patients had positive specimens for viral isolation. 91 cases of this positive were Enterovirus 71. The others were Coxsackievirus type A (A4, A6, A9, A10, A16); Coxsackievirus Type B(B1, B3, B4, B6) ; Echovirus and Poliovirus. Northern region of Thailand is the most common of HFMD cases. The subgenogroup of Enterovirus 71 were found B5, C1, C2, C4 and C5 which C4 is the majority of subgenogoup in 2008.

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- Enteroviruses surveillance in the patient with acute flacid paralysis in 2001-2005
- Molecular epidemiology of EV71 isolated in 2003 at Ha Tay Province
- Poliovirus antibody status in children 1-10 years olds in 2001

Laboratory Diagnosis of Enterovirus Infection in Patients with Acute Flaccid Paralysis and Hand Foot and Mouth Disease in the North of Viet Nam during 2001-2008

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During the period from 2001 to 2008, 1,486 cases with acute flaccid paralysis and 87 cases with HFMD were studied. The Stool specimens were treated with 10% chloroform and inoculated in cell cultures (AFP specimens/RD and L20B; HFMD specimens/RD cell). The throat swab specimens were extracted by RNA extraction Kit/Qiagen and then amplified by RT-PCR one step with Primer Oligo68 and EVP4. All positive specimens by RT-PCR were repeated by RT-PCR one step with Primer EV71 (159S/162A) and inoculated into RD cell line. All virus isolates were extracted and amplified by snRT-PCR (CODEHOP PCR) with primers (AN 32-34 for cDNA, SO224 and SO222 for PCR1; AN89 and AN88for PCR2), and were sequenced by sequencing reaction with BigDye Terminator v1.1, vl. 3,5 x sequencing buffer (Applied Biosystems) and each primer (F/AN89 and R/AN88). Results showed that: In patients with AFPs: 18.8% were positive with enteroviruses. Isolated enteroviruses contains 4 serogroups (81 echovirus divided into 18 serotypes in which the majority were E6,11,14,25 and 30 serotypes ; 29 CB viruses contained 5 serotypes in which the majority were CB5, and 22 CA viruses with 8 serotypes in which the majority were CA24; Poliovirus and EVs were at the lower rates).

In the HFMD outbreak in 2008: 35.6% were positive with enteroviruses in which EV71 accounted for 22.6% and CA16 were 71%. Only one specimen were positive with CA10.

Molecular epidemiology of 17 EV71 strains isolated in patients with AFP, HFMD in 2003, and during the period of 2005-2008 showed that: 17 EV71 strains isolated in the northern and central Vietnam in 2003, 2005 – 2008 were genetically grouped into the major EV71 genogroup C. Phylogenetic analysis of the EV71 strains in Vietnam, including the representative EV71 strains of each subgenogroup which were previously identified (A, B1-B4 and C1-C5), revealed that all of the isolated

EV71 strains from 2005 to 2008 shared to a new subgenogroup C5, distinguished from previously reported EV71 subgenogroups C4 (2003)

Serological epidemiology of EV71/IgG antibody from sera of healthy individuals showed that more than 50% humans >= 2 years old were infected EV71 virus in which 53% were in the age group 2 – 5; 71.2% were in the age group 6 – 10; 59.5% were 11 – 15 years old and 43% were >=16 years old.

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