Factors in the Emergence of Arbovirus Diseases
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Arboviruses and related viruses as emerging pathogens in Southeast Asia

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Summary - A decade ago, increased reporting of the spread or appearance of emerging pathogens was observed by the scientific community, and emerging diseases at the time were defined. In order to evaluate the importance of this newly recognized nosological concept, comprehensive analyses were performed on different ecological aspects of germs, the epidemiology of diseases and factors of emergence. Along with human diseases which were considered as new or emerging, animal and plant diseases were indicated as well. Emerging diseases of infectious and non-infectious origin were identified and a large group of vector-borne emerging viral diseases was recognized and considered of major concern with regard to public health. This article focuses on vector-borne viral diseases and related diseases that are a potential threat to the south-eastern region of Asia. In order to provide human and technical resources and establish a system of early detection of emerging viral diseases (EVD) in Southeast Asia, Mahidol University through the Center for Vaccine Development and Orstom through the Departement Santé proposed to join their efforts and develop a research project to study EVD as a potential threat to the human population of Southeast Asia. Goals and strategies of the project are: to develop an inventory of viruses of medical importance, along with their vectors and their hosts; to define natural transmission cycles of the virus and identify risk factors for humans and domestic animals; to design strategies for EVD prevention; and to provide training for scientists in the field of EVD.

emerging viral diseases / Southeast Asia / arbovirus / dengue

Introduction

As now observed worldwide, Southeast Asian countries have for almost a decade been experiencing an increase in frequency and spread of viral diseases. The concept of emerging viral diseases (EVD) was defined at the end of the 1980s when the scientific community witnessed the appearance of new pathogens and/or their dramatic spread in previously nonimmune populations or exempted zones [1]. EVD are considered as: a new disease caused by a new pathogen; a newly imported disease in a virgin population and/or area; a known disease with a new magnitude of epidemic manifestation in a given area.

EVDs appear in various ecological areas and latitudes, most of which involve a vector and/or a reservoir of virus. Of the 100 arbovirus that are pathogens for humans, at least 20 are regarded as potentially responsible for EVD [2]. Because of their epidemiological characteristics, some are considered as a real threat to the human population on a global level. While

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medical coverage and technical support permit more intensive surveys in the developed northern countries, the tropical zone appears less protected and studied. However, it is noteworthy that EVD of tropical origin have been clearly identified. It is recognized that biodiversity plays the same role for pathogens as for higher organisms, and tropical regions, particularly rainforests, can be considered potential reservoirs of as yet unknown viruses. Therefore, an inventory of pathogens and their ecology in the inter-tropical zones remains of primary importance for the early detection of potential emerging pathogens.

Emerging vector-borne viruses in Southeast Asia

In July 1995, the International Conference on Emerging and Reemerging Communicable Diseases and Impending Epidemics in Southeast Asia was held in Bangkok. From that meeting, contacts were made between the Center for Vaccine Development (CVD) at Mahidol University and Orstom, a French governmental institute for cooperative research and development, in order to coordinate efforts and propose a research programme for studying EVD in Thailand. During this first Asian meeting on EVD, experts identified and listed potential emerging or reemerging viral diseases for the region requiring investigation and survey (table I). Some were considered either as emerging or as a potential emergence threat for the region and were ranked as a current problem, a potential problem or as viruses with a human and/or domestic animal pathogenic potential.

A long-term arbovirus survey performed during the second part of the century, mostly in the tropical Africa and South America, resulted in the isolation of hundreds of new arboviruses – more than half the entire group of known arboviruses [3]. However, in the Southeast Asian region, limited systematic surveys have been undertaken and an exhaustive inventory of arboviruses and virus associated remains to be done. Even though some extensive studies have been done on specific viral pathogens (dengue viruses, dengue hemorrhagic fever [DHF]; Japanese encephalitis [JE] virus in several countries of the region (northern Thailand, southern Vietnam, Malaysia), there is a great need for specific studies regarding the local ecology and epidemiology of germs and diseases of other virus groups considered as potential threat for the human population worldwide *(Arenavirus, Bunyavirus, Filovirus, Hantavirus, Togavirus)*. Some viruses of these groups are known in Asia (Chikungunya, West Nile, Sindbis), some have been investigated *(Hantavirus)*, others appear more specific of that part

Table I. Emerging viral infection in Southeast Asia.

Immediate threat	*Potential threat*	*Potentially pathogenic for humans and/or animals*
HIV/AIDS	Hantavirus	Bat cave
Dengue	Yellow fever	Bebaru, Gethah
Hepatitis B,C,A,E	Arenavirus	Kyasanur Forest
Japanese encephalitis	Filovirus (Ebola-Reston like)	Langat
Measles	HTLV-I	Ross River
Influenza	HTLV-II	Sindbis
Poliomyelitis		Tembusu
Chikungunya		Wesselsbron
Herpes		

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of the world (Bebaru, Gethah, JE, Kyasanur Forest, Ross River) and deserve a special attention in the Indochina peninsula.

Within the frame of EVD here are few examples and specific questions relevant to Southeast Asia:

In Cambodia during the first 6 months of 1995, more than 2,800 cases of DHF were observed with 5% mortality. (Rathavuth, personal communication). Encephalitis of viral origin (spinal fluid clear) are observed every year and most of them can be related (serologically) to JE. A JE strain was isolated in Phnom Penh in 1995. The DHF, from a urban situation in 1985, changed to a more rural one after the two large outbreaks of 1987 and 1994 (Sun Lay, Phommasack, personal communication).

In Myanmar, DHF was recognized in 1970. In 1994 an outbreak of more than 7,000 DHF cases was recorded (Hla, personal communication).

Dengue epidemics seem to occur in Vietnam with an unexplained periodicity of 4 years (Duc Hien, Quang Ha, personal communication). More than 40,000 cases of DHF are reported every year. In southern Vietnam, due to unusual flooding of the Mekong River, 4,000 cases of DHF were suspected in 1996 in the delta. In 1993, an outbreak of hemorrhagic fever was observed in northern Vietnam. Differential diagnosis of DHF and JE was negative, and 57% of the population of 1,500 was infected, with 2% mortality (Thi Phuong Lien, personal communication).

Encephalitis and hemorrhagic fever are observed in Laos every year. However there is a desperate need for etiologic diagnoses in this country. Furthermore, a specific *Aedes aegypti* genotype seems to be associated with dengue virus transmission in this country (Hongvanthong).

More than 150,000 cases of hantavirus infection were identified in 1996, mostly in China (Wang Lee, personal communication).

Several viral-like epidemic manifestations (encephalitis, hemorrhagic fevers, dengue-like syndrome) have been observed and reported, without evidence of an etiologic agent, from northern Vietnam and Thailand on the Cambodia/Laos/Myanmar borders.

Emerging viral diseases in Thailand

Fevers of unknown origin (FUO) have been studied by several authors and mostly documented from hospitalized patients from the palearctic countries. Nevertheless, 22–37% of these fevers appear to be of infectious origin and 1/5 of them have a viral etiology [4]. In tropical regions, FUO, in conjunction with hemorrhagic syndromes and hepatitis syndromes, represent 1/3 of undiagnosed syndromes and are probably of viral origin. In tropical Africa (Central African Republic) we observed that a large proportion of FUO can be related to a viral or Rickettsial origin [5]. In 1993, 236,721 cases of pyrexia of unknown origin were reported in Thailand by the Center for Disease Control. By analogy with other tropical areas, we can expect that at least half of them are potentially of viral origin.

Serological evidence of hanta-like viruses in rodents and man were found in 1982–83 [6]. An original strain (Thailand virus) was isolated from the great bandicoot (*Bandicota indica*) in 1985; more recently, in 1995, a new Hantavirus, distinct from the Thai Hantavirus strain, was identified in the same rodent (Lee, Katrin, personal communication).

Two patterns of virus epidemiological activity (epidemic vs endemic) of JE are observed in Thailand [7]. Although strains can be genetically differentiated, no specific phenotypic characteristics of pathogenesis, virulence, infectiousness can be clearly identified.

The question of DHF manifestations remain unanswerable. Do the virus strains associated with DHF have a specific genotype? How can circulating strains generate a risk for DHF in novel population and areas? Does the dengue virus have a selvatic cycle? Greater knowledge of the viral genotypes circulating on the Thail borders and in surrounding countries is needed. Moreover, the spread of the virus needs to be analyzed regarding the vector competence, abundance and population genetics.

It as been hypothesized that Chikungunya (CHIK) virus has generated a parent strain of the o'nyong-nyong virus that affected millions of people in 1959 in Uganda and neighboring countries. Since CHIK epidemics have been observed in Thailand, they deserve special attention regarding the virus ecology and maintenance cycle. Such questions could be addressed by a comparative molecular analysis of Asian and African CHIK and o'nyong-nyong virus strains.

Kyasanur Forest disease (KFD) appeared in 1956 in India, affecting monkeys and humans in an altered environment. KFD virus seems to remain in a silent tick/rodent cycle until it suddenly strikes in an altered environment. Because of such silent cycles and the suddenness of the viral breakthrough, ticks are crucial in EVD investigations.

Several other tick-borne (Langat, Ntaya) or mosquito-borne (Tembusu, Semliki Forest, Bataï, Akonam) arboviruses are known to be present in Thailand and other countries in Southeast Asia [8]. Their ecology needs to be investigated regarding their potential as EVD.

The Reston virus, an Ebola-like virus, has been isolated from *Macaca mulatta* in the Philippines. Filoviruses appeared to circulate in monkeys in the Philippines, Indonesia and Thailand [9]. Ebola-Reston antibody-reactive sera have been found in monkeys and humans in Thailand. Such a situation leads to the question of filovirus strains circulating in the region as a potential risk for humans.

Most of the factors of viral disease emergence are associated with human behavior sensu lato. Dense, moving populations from Southeast Asia are known to be at risk for EVD. Travel, hygiene, urbanization, new technology and industry, and lack in public health management are generating EVD risk factors. Among these situations, the increase in the human population appears to be associated with the spread of dengue virus and the emergence of DHF, the number of hantavirus-infected rodents, contaminated soil, dry and windy seasons, human contact with rodents (farming activities, outdoor work), as well as poorly ventilated areas sheltering infected animals are major risk factors for hantavirus infection (Wang Lee, personal communication).

A fundamental task is to achieve a better knowledge about viruses with EVD potential, thereby improving ecological studies on the viruses and their vectors. The undertaking of such a task will promote the control and prevention by early detection of EVD in a given physical and human environment. The project described below is an attempt to pursue such goals.

The Research Center for Emerging Viral Diseases project

Goals and strategy

EVD as a potential threat for the human population of the Southeast Asian region will be studied under the codirection and joint guidance of the Center for Vaccine Development (Mahidol University, Thailand) and Orstom (based at the university). The aim of the project is threefold: development of laboratory facilities for implementation of a permanent laboratory-

and field-orientated research program on EVD; use of the program as a module for academic teaching and practical research training; use as a reference laboratory for the Southeast Asian region. A long-term objective will be to develop a regional network for the study and early detection of EVD in Southeast Asia.

The strategy will consist in identification of clinical cases of suspected EVD as well as establishment of a significant virus inventory, including vectors and hosts. The purpose of such study is to define natural transmission cycles and evaluate the risks of human infection.

The virology research laboratory will assist hospital- and dispensary-based routine survey of potentially threatening viruses and specific EVD. Laboratories will function at a national and regional level in conjunction with other laboratories specialized in the field of EVD around the world. Experimental virology will be carried out using appropriate security level.

The research programs

Laboratory and field-orientated techniques will serve as a support for training. Regarding clinical issues, two areas of research will be covered: a retrospective and prospective study of the syndrome and epidemiological manifestations of unknown etiology, and a prospective study by seroprevalence and virus isolation in targeted populations in a suspected endemic area. Syndromes such as dengue-like syndrome, hemorrhagic fever, renal syndrome or acute pulmonary syndrome and hepatitis will serve as a guidelines in the search of potential EVD. Each individual case will be explored, and an environmental study will take place in order to identify potential vectors and/or hosts.

As previously mentioned, priorities will focus on the understanding of specific virus ecology and disease epidemiology: the prevalence/incidence of hantavirus and the potential of the natural host ectoparasite as a vector of virus; the spread of hepatitis E virus in various Thai populations and the increasing incidence of hepatitis C over hepatitis B; the ecology of dengue and JE viruses, their vectors (population genetics) their reservoirs, and the changing clinical pattern of dengue infection; the prevalence and ecology of the Sindbis virus. Finally, a multicentric study on flavivirus vector competence of *A aegypti* will be developed in collaboration with laboratories in South America and West Africa.

Because of the prevalence of tick-borne viruses in Asia (1/3 of the known tick-borne viruses) a research program will address the question of viral disease transmitted by ticks to humans. Although *Rickettsiae* are not classified as viruses, their potential transmission by ticks will justify more detailed investigations once arboviral studies have been developed.

Training Program

Several approaches will be taken:

– Development of a practical research training program for young scientists, physicians and public health officers. Students involved in either a masters or doctoral project, or who are already in the post-doctoral stage, will compete for a research grant at the research center.

– Establishment of a regional EVD network of seminars and scientific exchanges, including fellowships for trainees from Thailand and abroad.

– An academic course on EVD for students from different universities in Southeast Asia.

– Seminars for the project directors of national EVD programs to inform and present the state of the art in specific domains of EVD relevant to the region.

Conclusion

Some of the expected results of the project developed at the research center on EVD in Thailand are: better knowledge of the ecology and epidemiology of EVD; development of tools for the diagnostic and epidemiological study of EVD and their transfer to other laboratories; complete study of pathogenesis, thus allowing the formulation of strategies for preventing diseases; virus phylogenetical studies, allowing a molecular epidemiological approach – eventually creating the potential for identifying a candidate vaccine. Finally, human resources will be identified for the development of an early system of EVD detection through a training program and will be involved in the development of a Southeast Asian network on EVD.

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