



EMERGING INFECTIOUS DISEASES IN SOUTH EAST ASIA : RESEARCH PRIORITIES

In 1997, the theme chosen by the WHO to celebrate the World Health Day was "Emerging Infectious Diseases: Global Alert-Global Response". That was as a wake-up call for the member countries to develop strategies to meet the challenges in combating emerging infectious diseases. There exist a widening gap between the capacity and capabilities of the member states to deal with emerging infections. The possibility of bridging this gap depends on how well international, regional and national collaborations can be forged.

Since 1973, close to 50 newly identified infectious diseases and syndromes have been recognized worldwide. Some have jumped from other species to infect humans (avian influenza, Nipah virus, Hendra virus, Hanta virus), others are transmitted through food (*Escherichia coli* O157:H7, variant Creutzfeldt-Jakob disease). Diseases such as West Nile fever and Rift Valley fever have spread to new geographical areas via vector. Some have geographical foci (*Neisseria meningitidis* W135, and Ebola, Marburg, and Crimean-Congo haemorrhagic fevers). SARS was identified in China in 2003, and soon spread to several countries.

The Role of Research

Disease surveillance is corner stone of response to emerging disease threats. Surveillance indicates where a disease has appeared and gives vital clues about how the

emergent infectious agent may spread in nature. After surveillance has brought attention to the problem, however, actual prevention and control measures ultimately require additional information provided by scientific research.

- Research defines the biomedical and behavioural factors influencing the emergence and spread of disease. Increased understanding of these factors will permit prediction of potential problems and application of preventive measures.
- Research in such diverse disciplines such as microbiology, epidemiology, molecular biology, and immunology is essential to the development of improved diagnostics for better surveillance and targeted treatment. Research in related fields, such as ecology and entomology can lead to alternative control strategies focused on vectors or reservoir hosts.
- Research identifies new opportunities that can be exploited to enhance infectious disease control. For example, research on the biomedical applications of new technological advances (such as remote sensing, computer modeling, etc.) may improve country's ability to predict future infectious disease outbreaks, thereby providing an early warning system.

Emerging Infections in South-east Asia

The recent emergence of a new strain (H5N1) of influenza A virus, the avian or bird flu, and the earlier outbreak

of SARS, underlines the importance of the Asia as an epicenter not only for influenza A viruses but also for other microbial agents. In late 1992, *Vibrio cholerae* 0139 appeared on the Indian subcontinent; and within a few months, it had spread to various countries far and wide¹.

But faced with reality of the burden of existing infectious disease almost on a daily basis, the countries of the South-east Asia region have not been able to give emerging diseases the priority it deserves. Much of the surveillance in the region is centered in a few well-established laboratories. In general there is inadequate expertise and infrastructure, insufficient funding, and lack of political will. It was only as a result of the activities of the Pacific Basin Respiratory Virus Research Group, that an excellent surveillance programme for respiratory viral infections is in place. If this small cluster of avian flu had occurred elsewhere, it would most likely have been missed².

Major interest and attention regarding emerging diseases in South-east Asia have been directed at zoonotic and vector-borne diseases. However, other diseases like HIV/AIDS, drug resistant malaria, shigellosis, typhoid and tuberculosis, hepatitis C and E, *etc.* have also received proper attention. Some of the major emerging infections are as follows:-

Enteroviruses

Enteroviruses are frequently associated with the hot and humid climate of tropical countries in South-east Asia. The viruses are responsible mainly for inapparent and mild infection, but occasionally they can give rise to infection of the central nervous system, resulting in aseptic meningitis and (rarely) paralysis; polioviruses are a good example. Hand, foot, and mouth diseases, caused by enteroviruses, such as coxsackie A16 and enterovirus 71, is common in many countries in the region. In a recent outbreak of hand, foot, and mouth disease in Malaysia, a new clinical entity of encephalomyelitis emerged, which resulted in several deaths among children under 5 years of age.

Molecular genetic studies of EV71 isolates have indicated that several distinct viral genotypes circulated in Peninsular Malaysia, Japan, Taiwan and other countries between 1997 and 2000³.

Dengue

Dengue is by far the most important arbovirus infection in South-east Asia. The haemorrhagic form of dengue fever, the dengue haemorrhagic fever (DHF), was recognized as a new disease in the Philippines in 1953 and has been seen in India, Malaysia, Singapore, Indonesia, Vietnam, Cambodia, and Sri Lanka. The rise of dengue in tropical and subtropical areas of the world is explained by factors

such as rapid population growth, expanding urbanization, inadequate municipal water supplies, and difficulties in refuse disposal. These lead to an abundance of new breeding sites for the mosquito vectors, while human migration patterns disperse vectors and viruses into new areas.

The resurgence of DHF in several countries where only dengue fever had been reported earlier has become worrisome. Sri Lanka reported its first outbreak in 1989, followed by cases in India and China. In Malaysia, where the disease is endemic, encephalitis cases associated with dengue viruses have been documented, and vertical transmission of the disease has also been reported in the last two years. Other unusual manifestations observed rarely include acute renal failure and hemolytic uremic syndrome. The emergence of such unusual clinical manifestations should also be monitored and documented in other dengue endemic countries².

Chikungunya virus

Chikungunya virus was relatively common in southern and south-eastern Asia in the 1960s. After causing outbreaks in India, Sri Lanka, Burma, and Thailand, it all but disappeared in India, Sri Lanka, Burma and Bangkok⁴. However, localized outbreaks and sporadic cases continued in Burma, Thailand in the 1980s. In addition, the virus spread into Indonesia for the first time from 1982 to 1985. Outbreaks occurred in Thailand in 1995 and Malaysia in 1998 to 1999.

Emerging zoonotic viruses

A number of viruses have emerged from fruit bats (flying foxes), particularly members of the genus *Pteropus*, over the past 10 years. These include Hendra and Nipah viruses.

Nipah virus

A major outbreak of disease in pigs and humans in the Malay Peninsula from September 1998 to April 1999 resulted in 265 infected persons, 105 of whom died, and the eventual destruction of about 1.1 million pigs⁵. The predominant clinical syndrome in humans was encephalitic rather than respiratory, with clinical signs including fever, headache, myalgia, drowsiness, and disorientation, sometimes proceeding to a coma within 48 hours. Most infected persons had a history of direct contact with live pigs, and most were pig farmers. Epidemiologic evidence suggested that the disease had been spread primarily by pigs that were transported between farms or to other regions.

Preliminary research on the new virus, subsequently named Nipah virus, revealed that it had ultrastructural, antigenic, serologic, and molecular characteristics similar to Hendra virus.

Surveillance of wildlife species for evidence of the origin of Nipah virus was an integral part of the outbreak investigation. Knowing the similarities between Nipah virus and Hendra virus, attention was focused on surveillance of bats. In common with most countries in South-east Asia, Peninsular Malaysia has a great diversity of bat species. Antibodies that neutralize Nipah virus were found in more than 20 bats from five species³.

Research Priorities in Emerging Infectious Diseases

Research is needed for

- (i) Understanding environmental factors which facilitate emergence, maintenance and transmission of these diseases
- (ii) Studying the evolution of pathogenic infectious agents resulting in changes in infectivity, virulence transmissibility and adaptations
- (iii) Knowing host factors influencing emergence of new infection and their transmission
- (iv) Development of tools for diagnosis, management, control and prophylaxis
- (v) Training and infrastructure for responding to emerging diseases
- (vi) Information sharing on emerging infections
- (vii) Development of research-based evidence to influence policy modifications

Research on environmental factors

Natural environmental changes are known to influence disease transmission—especially the vector-borne diseases, and zoonotic diseases.

Natural calamities like earthquakes, cyclones, floods and droughts might lead to emergence or re-emergence of infectious diseases. Examples of such research include:

- Effect of deforestation and use of land for cultivation and/or human settlement: as settlers come in contact with vectors and are exposed to large number of new viral, parasitic, and bacterial disease agents. In India, for example, people going to forests to collect wood were bitten by ticks and came down with Kyasanur forest disease.
- Study impact of developmental projects – construction of dam and irrigation canal, laying of railway lines: Malaria has spread along the irrigation canal in the desert areas of Rajasthan in India, like wise the laying of Konkan railway lines has carried the malaria vector in areas where malaria did not exist.
- Effect of drought followed by heavy rains.
- Global warming and its effect on span of life-cycle, flight ranges, *etc.* of vectors.

- Expanded research on natural history of disease in simulated conditions
- Study of urban ecology: The reappearance of plague in some parts of India, as also cholera and dengue is due, in part, to rapid slums around mega cities. Tires and plastic containers collect water and may act as breeding sites for mosquitoes, and this may, in part, be responsible for spread of dengue in many countries of South-east Asia.
- Define ecological factors that influence the possibility of invertebrates to serve as vectors
- Determine means of transmission for which risk factors are poorly understood, define ‘at risk’ populations
- Pathogen transmission between wild and domestic animals.

Evolution of pathogenic infectious agents

- Research to identify genetic coding sequences of important viral, bacterial parasitic agents to help develop new treatments/vaccines.
- Research on molecular genetics and biochemistry to identify critical pathways and functions involved in the micro-organisms replication and development. The components of these pathways could serve as new targets for new antimicrobial drugs.
- Research on microbial physiology to understand the mechanism used by pathogens to affect drug resistance to develop novel strategies to overcome these phenomena.
- Application of molecular techniques to understand the virulence and epidemiology of microbes by providing ‘finger-prints’ which help in tracking the spread of infection.
- Intermicrobial interactions to increase understanding of emergence of new pathogens or new disease manifestation.
- Use of molecular epidemiology to establish transmission pattern of diseases across national boundaries.

Host factors

- Rapid transportation has been blamed for the spread of diseases, and this is especially so in countries in South-east Asia region. Tourism is an important industry in South-east Asia, and series of conferences on travel medicine have highlighted the problems, particularly in infectious diseases. Another group of people responsible for vast movement between countries in the region is that of migrant workers. In Malaysia, an estimated 1.7 million workers are migrant workers, of which only 1.2 million have entered legally. Most of the

workers are from Indonesia, Myanmar, Philippines and Pakistan, and they work in the agricultural sector as well as in construction and domestic services. Workers coming legally undergo a medical examination that includes screening for some infectious diseases. Diseases associated with migrant workers are chloramphenicol-resistant typhoid, multidrug-resistant TB, leprosy, malaria, HIV/AIDS, and filariasis. In 1993, the first case of kala-azar caused by *Leishmania donovani* was reported in Bangladeshi migrant worker in Malaysia, and since then, four other cases have been identified, all of them in Bangladeshi workers. This disease had not been present in Malaysia².

- Wide-spread use and in some cases abuse of drugs can result in the selection of resistant organisms. A large number of organisms are becoming resistant to antibiotics. In some countries irrational and indiscriminate use of potent medicines is the result of failure to enforce pharmacy laws. These drugs can often be purchased without a prescription. Because of financial constraints the sick people often cannot buy total requirement, and this chronic under-dosing selects drug resistance strains.
- Effects of immuno-suppression, resulting in decreased resistance to new infections, and possibility of reactivation of the latent infections.
- Molecular mechanisms responsible for development of long term sequelae of infections
- Studies on identification of targets and mechanisms of protection for immune responses; identification of pathogen and host factors responsible for eliciting non-protective or detrimental immune response; and microbial adaptation to host immune response.

Development of tools

Translation of recent research discoveries to new and improved vaccines, drugs and other control strategies require dedicated/committed resources.

- Establishing and strengthening surveillance system for infectious diseases. Surveillance indicates where a disease has suddenly appeared and gives vital clues about how the emergent infectious agent may spread.
- Development of new field-applicable diagnostic tests to facilitate surveillance
- Research on biomedical applications of new technology such as remote sensing, geographical information system (GIS) to improve ability to predict future infectious disease outbreaks.
- Development of vaccines to block the transmission of microbial pathogens, genetic alteration of a vector to prevent a pathogen from replicating within it.

- Development of vaccines for use in wild animal reservoirs.
- Detecting and limiting environmental sources of contamination, such as water supplies.
- Validate current epidemiologic and modeling studies to assess the effectiveness of control methods in regions where drug resistance is a problem
- Development of models to demonstrate the impact of delays in implementing outbreak control measures and increasing the number of index cases on the incidence of cases of simulated outbreaks.
- Development of animal models of emerging/re-emerging human diseases to facilitate development and testing of new vaccines and drugs. These should focus on newly emergent pathogens for which no convenient or representative models exist and on models of immunocompromised host.
- Application of mathematical models for understanding transmission dynamics
- Predictive microbiology for food-borne infections: While considerable progress has been made in defining philosophic approaches and experimental protocols for growth model development and many models have been developed and published, more validation studies are required, particularly involving independent and industry-based trials. More emphasis should be placed on modeling the death kinetics of food-borne pathogens with low infective doses⁶.

The development of techniques to measure constraints such as water activity, pH, or redox potential on a microscale might provide useful information for a complex food such as salami. This would allow definition of the role of the microenvironment in determining microbial behavior. The concept of a microenvironment is well developed in soil microbiology⁷ but has been neglected in food microbiology.

Models are normally developed under static conditions (growth rates and lag times are measured at a series of set temperatures, water activity values, and pH levels), and the results are combined to describe the effects of each factor or a combination of factors on population development. Subsequently, models must be validated in foods under conditions that mimic situations encountered in normal practice, *eg.* decreasing temperature and water activity during active chilling of meat carcasses or fluctuating temperatures during the distribution and storage of many food commodities.

Methods to define the physiologic status of food-borne contaminants under various conditions need to be developed. This will require observations on individual cells or small populations of cells either directly by microscopy or an indicator of single-cell metabolic activity⁸.

Social factors

Research questions identified above are important for the understanding and eventual control of emerging infectious diseases. Yet unless the contribution of social inequalities is examined the interventions are unlikely to have the desired results. This requires research that is best done in a multi- and trans-disciplinary collaboration. Social inequalities have influenced not only the distribution of emerging diseases, but also the course of disease in those affected by them.

What are the precise mechanisms by which these diseases come to have their effects in some bodies but not in others? What propogative effects might social inequalities per se contribute?

Many political borders serve as semipermeable membranes, often quite open to diseases and yet closed to the free movement of cures. Thus many inequalities of access be created or buttressed at borders, even when pathogens cannot be so contained. Research questions might include, for example, What effects might the interface between two very different types of health care systems have on the rate of advance of an emerging disease? What turbulence is introduced when the border in question is between a rich and a poor nation?

Methods and theories relevant to the study of borders and emerging infections would come from disciplines ranging from the social sciences to molecular biology: mapping the emergence of diseases is now more feasible with the use of restriction fragment length polymorphism and other new technologies⁹.

Training and Infrastructure Needed for Research

Expertise and infrastructure for detecting and responding to infectious diseases outbreaks needs to be strengthened. Setting up a broad-based, interdisciplinary research and research training programme covering multiple aspects of infectious diseases, such as molecular epidemiology, population biology, ecology and environment, molecular pathology, electron microscopy, *etc* is needed. These include:

- Improved training for scientists, clinicians, public health professionals who can be mobilized to respond to these threats.
- Availability of laboratory with adequate bio-safety levels.
- Training of staff to work in high/maximum containment laboratories.
- Stable financial support.

Networking

Trading blocks, realizing the strategic importance of threats are concerned about emerging diseases. Like the

European Union, the Asia Pacific Economic Cooperation (APEC) has undertaken an initiative in combating emerging infections. The APEC Emerging Infectious Network is building on an existing internet based educational network (APEC Edu Net). This network permits scientists and policy makers to share information and combat emerging infectious diseases more effectively through surveillance, prevention, research and control measures. The Emerging Infectious Network (EI Net) includes project information, surveillance data, policy discussions, prevention guidelines¹⁰.

Human networking is as important as technology based networking in addressing emerging infections. There is a need to have a treaty basis to support this inter-country collaboration, hence MOUs are needed to facilitate sustainable surveillance information flow and scientific cooperation. Similar networks need to be developed between various agencies and institutions involved in research in emerging infections to share their experiences, data and concerns. A regional network of networks would help tremendously in sharing of information.

International Collaboration

The international dimensions of emerging infectious diseases are readily understood. Diseases do not respect political borders, and geographical boundaries. Oceans and mountains can be easily crossed in times of high-speed aircraft travel. The threat of emerging infections can no longer be seen as of one country or a region. The recent example of SARS outbreak has shown that what appeared at first a problem of a few countries in Asia became a global emergency. The SARS epidemic also demonstrated the importance of world-wide surveillance and response capacity to address emerging microbial threats through timely reporting, rapid communication, and evidence-based action. The needs of international collaboration and partnerships among clinical, laboratory, public health and veterinary communities were emphasized.

Can the countries redirect substantial effort towards the control of emerging infections without diluting their commitment to communicable diseases of current public health concern?

For early detection of an outbreak of an emerging infectious disease an international collaboration is required to improve the regional and national infrastructure for surveillance, strengthen public health services and support training in epidemiology and laboratory techniques. The surveillance would provide the background data against which uncommon events can be identified.

International collaboration would also be needed to develop standard surveillance guidelines, internationally

References

1. Basu, A., Garg, P., Datta, S., Chakraborty, S., Bhattacharya, T., Khan, A., Ramamurthy, T., Bhattacharya, S.K., Yamasaki, S., Takeda, Y. and Nair, G.B. *Vibrio cholerae* OBT in Calcutta, 1992-1998: Incidence, antibiograms and genotypes. *Emerg Infect Dis* 6:139, 2000.
2. Lam, S.K. Emerging Infectious Diseases – South-east Asia. *Emerg Infect Dis* 4: 145, 1998.
3. Mackenzie, J.S., Chua, K.B., Daniels, P.W., Eaton, B.T., Field, H.E., Hall, R.A., Halpin, K., Johnsen, C.A., Kirkland, P.D., Lam, S.K., McMinn, P., Nisbet, D.J., Paru, R., Ryke, A.T., Ritchie, S.A., Siba, P., Smith, D.W., Smith, G.A., Vanden Hurk, A.F., Wang, L.F. and William, D.T. Emerging viral diseases of South-east Asia and the Western Pacific. *Emerg Infect Dis* 7: 497, 2001.
4. Pavri K. Disappearance of Chikungunya virus from India and South-east Asia. *Trans R Soc Trop Med Hyg* 80:491, 1986.
5. Chua, K.B., Bellini, W.J., Rota, P.A., Harcourt, B.H., Tamin, A., Lam, S.K., Ksiazek, T.G., Rollin, P.E., Zaki, S.R., Shieth, W., Goldsmith, C.S., Gubber, D.J., Rochrig, J.T., Eaton, B., Gould, A.R., Olson, J., Field, H., Daniels, P., Ling, A.E., Peters, C.J., Anderson, L.J. and Mahy, B.W. Nipah virus: A recently emergent deadly paramyxovirus. *Science* 288: 1432, 2000.
6. McMeekin, T.A., Brown J., Krist, K, Miles, D., Neumeyer, K., Nichols, D.S., Olley, J., Presser, K., Ratkowsky, D.A., Rosst, Salter, M. and Soontranon, S. Quantitative microbiology: A basis for food safety. *Emerg Infect Dis* 3: 541, 1997.
7. Madigan, M.T., Martinko, J.M. and Parker, J. Microbial ecology. In: *Brock Biology of Microorganisms*. 8th edition (Chapter 14). *Prentice Hall*, New Jersey, p.534, 1999.
8. Baranyi, J., Robinson, T.P., Kaloti, A. and Mackey, B.M. Predicting growth of *Brocothrix thermosphacta* at changing temperature. *Int J Food Microbiol* 27: 61, 1995.
9. Farmer, P. Social inequalities and emerging infectious diseases. *Emerg Infect Dis* 2: 259,1996.
10. Kimball, A.M., Horwitch, C., O'Carroll, P., Arjoso, S., Kunanusont, C., Lin, Y.S., Meyer, C., Schubert, L. and Dunham, P. APEC Emerging Infectious Network: Prospects for comprehensive information sharing on emerging infections within Asia Pacific Economic Cooperation. *Emerg Infect Dis* 4: 472, 1998.
11. Hein, K. Health policy implications of emerging infections. *Emerg Infect Dis* 4: 379, 1998.
12. The NIAID Research Agenda for Emerging Infectious Diseases. *National Institute of Allergy and Infectious Diseases*. National Institutes of Health, Bethesda, USA, July 1996.

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