Asia-Pacific
Economic Cooperation

Roadmapping Converging Technologies To Combat Emerging Infectious Diseases

Bangkok, Thailand

A Project of the Asia-Pacific Economic Cooperation (APEC)
Industrial Science and Technology Working Group (ISTWG)

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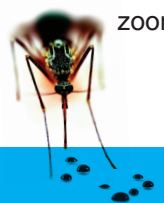
Acronyms

	Acronyms
acquired immune deficiency syndrome	AIDS
APEC Center for Technology Foresight	APEC CTF
Asia Pacific Economic Cooperation	APEC
National Center for Genetic Engineering and Biotechnology	BIOTEC
bovine spongiform encephalopathy, known as “mad cow” disease	BSE
emerging and re-emerging infectious diseases	ERID
emerging infectious diseases	EID
enzyme-linked immunosorbent assay	ELISA
global influenza surveillance network	GISN
global information system	GIS
global positioning system	GPS
high performance computing	HPC
high-throughput sequencing	HTS
human immunodeficiency virus	HIV
Industrial Science and Technology Working Group	ISTWG
loop-mediated isothermal amplification	LAMP
modeling and simulation	M+S
nanotechnology, biotechnology, information technology and cognitive science	NBIC
National Electronics and Computer Technology Center	NECTEC
National Institute for Science and Technology Policy	NISTEP
polymerase chain reaction	PCR
prevention of spread	PoS
preventive measures	PM
radio frequency identification	RFID
severe acute respiratory syndrome	SARS
SMart Amplification Process	SMAP
surveillance & detection	S&D
Treatment	Tr
ubiquitous computing – network systems	UC-NS
World Health Organization	WHO
zoonotic emerging infections diseases	ZEIDs



Foreword

Infectious diseases account for a quarter of all human mortality but in developing countries this rises to one in two deaths because of poverty, limited access to health care, drug resistance and a changing environment. Infectious diseases of crops and livestock cost the global economy uncounted billions of dollars every year. According to the World Bank, the 2003 severe acute respiratory syndrome (SARS) epidemic, which killed less than 1000 people, was responsible for an estimated 2% fall in gross domestic product across East Asia and an influenza pandemic could kill millions of people and cost about $900 million globally in a single year. Because of the extremely large social and economic disruptions caused by an increasing range of established and emerging infectious diseases there is a need to ensure that APEC economies are well positioned to deal with future emergencies.

With this in mind, the APEC Center for Technology Foresight (APEC CTF) in 2006 proposed a foresight study on new technologies and approaches which are needed to combat these threats, to reduce costs of treatment and to improve the human and animal health situation in both developed and developing economies of APEC. The time horizon was proposed to be beyond 2017. The study would use the techniques of bibliometric research, scenario creation and technology roadmapping.

The aim was to examine the opportunities arising from the convergence of a number of new technologies. In particular, the development of nanotechnology provides the ability to engineer matter at the nanoscale, molecular level, comparable to the size of cells and it provides a powerful driver of change for approaches to combating emerging infectious diseases when linked to genetics, biotechnology, information technology and bioinformatics.

After being submitted to the due process in the APEC Science and Technology Working Group (ISTWG), the study was approved and additional funding was made available from the APEC Central Fund to complement the funding from APEC CTF and other co-organizers. It was recognized at an early stage that the APEC Health Task Force had a strong interest in this area and contact was established.

The study has involved a bibliometric search, online survey, three interactive workshops and a symposium, namely:

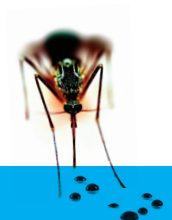
1. Bibliometric search and online survey over the period October 2006 to January 2007.
2. Scenario workshop held in Phang Nga, Thailand during 5 - 7 February, 2007.
3. Technology roadmapping workshop held in Tokyo, Japan during 22 - 24 May, 2007.
4. Technology roadmapping workshop held in Taipei, Chinese Taipei during 24 - 26 October, 2007.
5. Symposium held in Bangkok, Thailand during 13 - 14 December, 2007.

The strong support and hospitality of the host institutions is greatly appreciated.

The workshops and the symposium have been strongly supported by presentations at the meetings while a number of experts have contributed position papers on relevant areas. These have summarized in the report while all the available material has been collected and made available in the attached CD-ROM. The co-sponsors are particularly grateful to the authors and speakers and their organizations which enabled them to devote considerable time and effort to the study.

The co-sponsors would like to thank the numerous participants (roughly 35 to 40 in each of the workshops and 91 at the final symposium) from about half the economies in APEC who gave their invaluable time and experience to make the meetings successful and productive.

The APEC Center for Technology Foresight



Acknowledgement

This project could not be achieved without a great deal of helps and supports from many organisations and people. Firstly, the Center would like to acknowledge Asia-Pacific Economic Cooperation (APEC) and the National Science and Technology Development Agency, Ministry of Science and Technology, Royal Thai government for the very precious funding and supports towards the project.

Special thanks must be expressed to National Institute of Science and Technology Policy (NISTEP) Japan, the National Taiwan University and the National Science Council, (Chinese Taipei) for organising and supporting technology roadmap workshops in Tokyo Japan and Taipei, Chinese Taipei, respectively. Gratitudes are also given to all the authors of the six converging technologies chapters. They are: Prof Greg Tegart, Prof Michiaki Masuda, Dr Yoshiko Okamoto, Dr Stephen Prowse, Dr Piyawut Srichaikul, Dr Chaichana Mitrpant, Dr Parntep Ratanakorn, Dr Anan Jongkaewwattana and Mr Jack Smith.

Many appreciations are given to Japan who co-proposed project to APEC and all of the co-sponsoring economies: Australia, Canada, China, Korea, Malaysia, New Zealand, The Philippines, Russia, Chinese Taipei, USA and Viet Nam. The Center is grateful to Dr Richard Silberglitt of the Rand Corporation who has in particular given ideas and suggestions throughout the project, Dr Suthee Phoojaruenchanachai of NECTEC and Dr Nathasit Gerdsri of Mahidol University who led the facilitation of small group discussions in workshops. Last but not least, the Center would like to acknowledge, with much appreciation, all the participants to this project for all the ideas and discussions from the workshops and symposium.

Executive Summary

In the globally-linked world of the 21st century, policymakers are being forced to make far – reaching decisions at short notice, often without the full background information being available. An example of this situation is the response of economies to sudden outbreaks of infectious disease, increasingly of new types and unknown origins. Thus more new diseases have emerged in the past twenty years than in the previous fifty years with a majority of these originating in wildlife. Some of these have the potential to spread rapidly and to cause major epidemics, even pandemics.

There is thus an urgent need to identify new technologies and approaches which can be used to deal with outbreaks of emerging infectious diseases. Because there are a variety of disciplines involved in dealing with disease outbreaks it is important to ensure that there is productive interaction between them. This project has used Foresight as a systematic and participatory approach to develop an accelerated technological response to combating emerging infectious diseases.

The concept of converging technologies has been developed recently to describe the convergence of technologies and knowledge systems in pursuit of a common goal. In this project, specialists from a broad range of disciplines have been brought together in a series of workshops across the APEC region to share their knowledge and to apply techniques and results from the fields of information technology, nanotechnology and biotechnology to a better understanding of preventive measures, surveillance and detection and treatment and spread of emerging infectious diseases.

Based on a bibliometric study, scenario creation has been used to provide a framework for understanding the factors involved in the initiation and propagation of disease outbreaks and for identifying the critical technologies needed for dealing with them. The collective wisdom of the specialists has then been used to develop technology roadmaps which show how selected areas such as vaccines, diagnostics, ubiquitous computing, drugs, modeling and simulation and tracking can be improved over time to enable a more effective response to disease outbreaks.

The aim was to develop ambitious, but realistic, visions for the selected areas which would assist planning for future developments by industry, researchers and policy makers in the time frames of short (2007-2012), medium (2012-2017) and long term (beyond 2017). Each of the selected areas has specialized needs for continued

R&D and for training of technical and scientific personnel. Further, each of these is an essential component of building effective national, regional and global strategies to combat emerging infectious diseases. The weakness of any one component will put the whole system at risk.

The major conclusions of the study are:

- A life cycle model has been used to study the factors involved in initiation and spread of emerging infectious diseases namely, preventive measures, surveillance and detection and treatment and prevention of spread and to guide the development of responses in controlling these factors.
- This model can be linked to six significant technology domains namely, vaccines, diagnostics, ubiquitous computing, tracking, modeling and drugs. Each of these provides opportunities for converging technologies to make significant contributions to R&D and commercialization of devices and systems.
- Technology roadmaps have been developed for each of these domains to provide the basis for national and regional strategies for combating emerging infectious diseases.

The significant findings for each of the domains are:

- **Ubiquitous computing**-the concept of smarter information collection and management is an integral part of adoption of new processes and tools. Increased effort is needed to improve the automated analysis of surveillance data to enable early detection of outbreaks. Information technology is an integral part of developments in all the domains.
- **Diagnostics**-a range of tools to enhance capability in these areas needs to be developed specifically for the Asia-Pacific region, particularly focused on low cost, portability and rapid information flow.
- **Treatments**-more effort is needed on the development of therapeutic drugs for more effective risk management, even for those infectious diseases for which vaccines are available.
- **Modeling**- availability of realistic models can assist policy makers in developing options for coping with out breaks but they cannot be used in real time when input data are changing rapidly.
- **Tracking**- miniaturized systems are being developed to track both animals and humans but standards and protocols are needed to enable tracking across national boundaries.

- **Vaccines**-vaccine development, production and delivery are essential components of any strategy to combat EID and must be strongly supported. New approaches based on genetic manipulation and molecular design will allow more rapid development of vaccines.

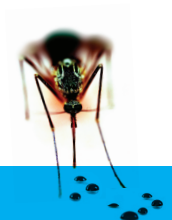
- The practical application of the concept of converging technologies in this project has created a new network of knowledgeable and concerned scientist and technologists in the APEC region. This can provide a focus for further co-operation.

- There is need for co-ordination of collaboration and sharing of information, facilities and training in combating EID across the APEC region. The APEC structure may provide a route to developing this co-ordination.

- The application of these new technologies in developing economies needs to be undertaken with great care, recognizing that there are major infrastructural, cultural and social differences. The "people factors" are crucial features of disease management through all phases of the life cycle model from detection to response.

- The translation of research outputs into policy is of critical importance. Politicians have to make decisions on the basis of available information which is often imperfect and hence the prompt and efficient transfer of information from the research environment into the policy environment is a critical component of effectively combating EID.

This project is a contribution to the better understanding of the provision of accelerated technological responses to combating EID in the APEC region and of the role of science and technology in providing those responses through the concept of converging technologies. However it is only a beginning and there is a need for further action by individual economies and by APEC itself as a co-ordination body to ensure that the region is adequately prepared for the outbreaks of emerging infectious diseases that will inevitably occur in the future.



Part I: Extended Summary

Chapter One: Introduction

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Infectious diseases account for a quarter of all human mortality but developing countries have a disproportionate share because of poverty, limited access to health care, drug resistance and changing food supplies due to impact climate change on land and water supplies. While SARS and avian influenza have attracted major attention in recent years there are other diseases which have emerged and also present threats to humans and animals.

More new diseases have emerged in the past 20 years than in the previous 50 years with a majority of these originating in wildlife. Further, old diseases such as dengue and foot-and-mouth disease have re-emerged to cause costly epidemics. Eight categories of infectious diseases have been identified as potential threats.[1]

These are:

- New diseases such as SARS and BSE with variants such as H5N1;
- Infections becoming resistant to treatment such as tuberculosis and Staphylococcus aureus;
- Zoonoses: i.e. infections transferring to humans from animals such as SARS, avian influenza, plague;
- HIV/AIDS, tuberculosis and malaria;
- Epidemic plant diseases;
- Acute respiratory infections;
- Sexually transmitted diseases and
- Animal diseases.

The categories are not mutually exclusive but illustrate the wide range of threats.

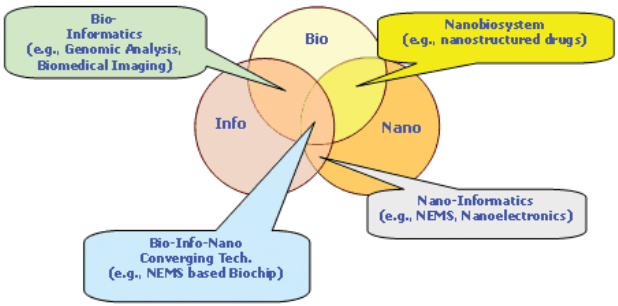
The world health sector continues to seek new technologies and approaches which are needed to combat these threats, to reduce costs of treatment and to improve the human and animal health situation in both developed and developing countries. As an example, recognition of the role of information technology provides a powerful driver of change for approaches to bio-security when linked to genetics, biotechnology, nanotechnology and bioinformatics.[2]

Recently, the concept of **converging technologies** has emerged in the USA and in Europe, emphasizing productive interactions between previously separate fields of research and technological development. Such shifts can result in new technological possibilities, with potentially revolutionary impacts associated with changing innovation patterns, industry structures and broader developments in society. It has been proposed that a new paradigm is developing in the 21st century based on the combination of nanotechnology, biotechnology, information technology and cognitive science (NBIC) and that these converging technologies could radically change society, economy and culture in the next 20 years.

Areas suggested are: societal productivity; security from natural and man-made disasters; providing sustenance for an ageing population; combating environmental degradation; promoting sustainable development; and creating capabilities for managing international crises

In the USA the term "converging technologies" was first used in a December 2001 workshop organized by the US National Science Foundation and the US Department of Commerce entitled "Converging Technologies for Improving Human Performance"[3]. This workshop proposed the concept of NBIC and discussed possible applications to human health and performance. Subsequently several conferences on specific applications have been held in the US [4-6].

In Europe the concept of NBIC was studied by a High Level Expert Group which produced a report in 2004 directed to the application of converging technologies to development of a European knowledge society [7]. This report contains the pragmatic definition: "**Converging technologies are enabling technologies and knowledge systems that enable each other in pursuit of a common goal**". A Knowledge NBIC project focused on a study of the patterns of knowledge production of the four key fields was launched in 2006. The concept has been extended in the Seventh Framework Program to the possibilities at the interface of micro-nano systems and the living world [8].



Source: Suthee Phucharoenchanachai, NECTEC (2005)

Figure 1: illustrates how nano-, bio- and info- technology can interact in biomedical applications. In the present study we have applied the concept of converging technologies to combating emerging infectious diseases. The study has highlighted the importance of interdisciplinary approaches that cross traditional intellectual boundaries in dealing with emerging infectious diseases.

Thus a better understanding of patterns of infectious diseases needs input from anthropology, economics and climatology supported by statistics and mathematics. The mechanisms of animal-human transmission need input from medicine and veterinary medicine coupled to virology, bacteriology, mycology and parasitology. Vaccine development and delivery can be speeded up using genetics, nanotechnology, molecular biology and bioinformatics. Moreover health systems research using social sciences, epidemiology and anthropology is needed to understand how new technologies can be used most effectively from the viewpoints of the needs, expectations, capabilities and cultural sensitivities of the end users.

Conduct of the Project

The project was organized into two phases. Phase I was designed to identify the potential issues related to emerging infectious diseases. Those issues were such as the trends of potential infectious diseases, the timing of emergence of those diseases, the level of severity of the impacts from the spread of those infectious diseases to communities, etc. Phase II was designed to take the findings from Phase I to determine the possible preparation for the future research and development needed in managing, preventing, or combating emerging infectious diseases.

To complete the objective in Phase I, a combination of literature review/bibliometric analysis and online surveys were conducted to preliminarily capture the trends of infectious diseases. The publication trends were analyzed by using the medical databases of MEDLINE, to present the potential trends of emerging infectious diseases. Then, an online survey was launched to get international experts involved in reviewing the identified trends of emerging infectious diseases. After the survey completion, a

face-to-face workshop for scenario planning was organized at Phang Nga in Thailand on 5-7 February 2007. Using scenario creation techniques, 33 experts from 7 APEC member economies shared their views about the severity of the impacts from the spread of emerging infectious diseases and identified the key research domains which the community of medical experts should emphasize so that those diseases can be effectively prevented, managed, or combated.

In Phase II, the objective was to determine directions for future research and development so that APEC member economies can prepare themselves ready to respond to the region's needs. To achieve this objective, the technology roadmapping technique was applied to analyze the linkage between the development of supporting technologies and the future changes of medical requirements in each research domain as identified in Phase I. Two roadmapping workshops were organized at Tokyo in Japan on 22-24 May (42 experts from 9 economies) 2007 and at Taipei, Chinese Taipei on 24-26 October 2007 (41 experts from 8 economies) to enable infectious disease specialists and technologists to work together in completing the roadmap development.

Experts discussed the future changes of medical requirements in each research domain, the types of supporting technologies needed, the key challenges that could possibly hinder the development progress and R&D activities. At the end of Phase II, a final symposium was arranged in Bangkok on13-14 December 2007. 91 experts from over 14 APEC economies and covering many disciplines and sectors discussed a longer term perspective to enhance the region's capacities that contribute to the successful prevention and management of emerging infectious diseases.

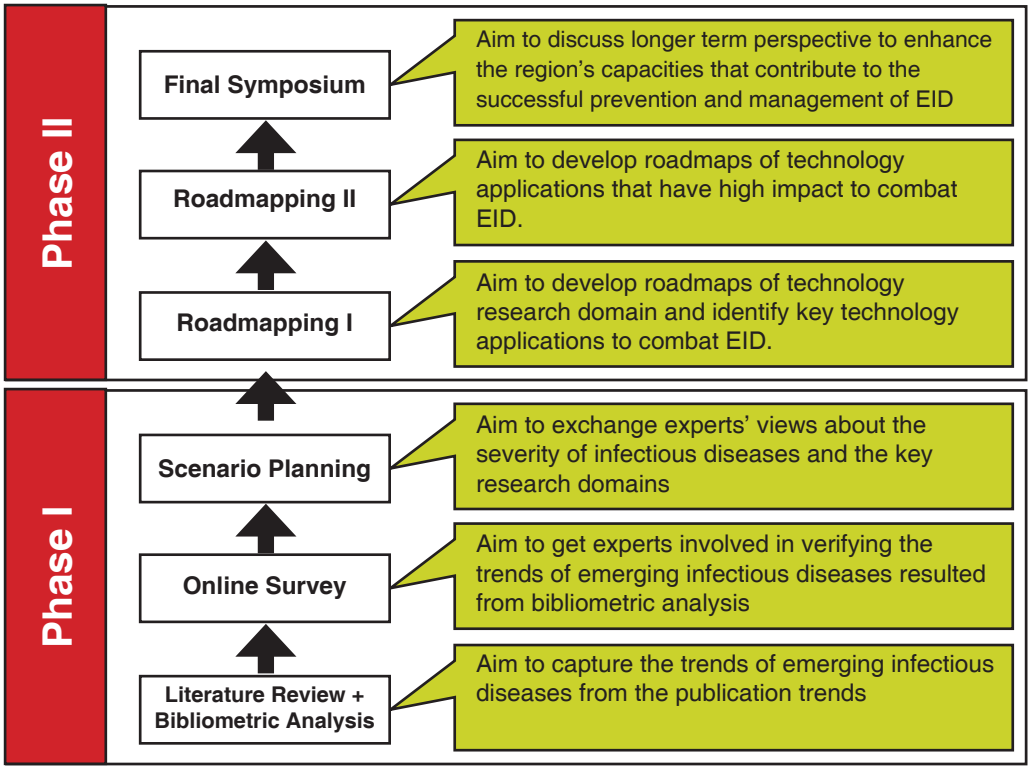


Figure 2: Information flow through the two phases

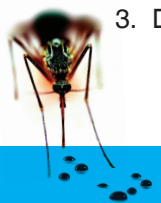
Scenario-Based Futures

Pre-workshop Activity

Over the period November 2006 to January 2007 an extensive bibliometric analysis was carried out by the National Institute for Science and Technology Policy (NISTEP) in Japan and by the National Electronics and Computer Technology Center (NECTEC) and APEC CTF in Thailand. A significant reference source was the UK Foresight study on Infectious Diseases.[9]

Based on this analysis, three research domains related to combating EID were identified:

1. Bioterrorism and Surveillance System
2. Earth and Climate Observation
3. Detection, Diagnosis and Identification.



An on-line questionnaire was constructed around these domains and was mounted on the APEC CTF website. A number of potential technologies were offered for consideration and ranking on the basis of level of impact. Experts from across the region made responses. The results of the survey were:

1. Bioterrorism & Surveillance System

1.1 To have a global outbreak alert and response network

1.2 To monitor pre diagnostic health-related data for early detection of outbreaks. (Public health surveillance technology)

1.3 To support public health analysis in interpreting surveillance data and identifying disease outbreaks

1.4 To estimate impact of attack

1.5 To control airborne pathogens.

2. Earth and Climate Observation

2.1 To improve understanding and accuracy of planning, prevention and prediction of outbreaks

2.2 To have an early warning system based on seasonal forecasting models

2.3 To improve tagging of animals in order to assist with monitoring and management of animal movements

2.4 To improve geographical data

3. Detection, Diagnosis and Identification

3.1 To have a rapid and sensitive real-time diagnosis for infectious diseases

3.2 To share large databases for disease I.D.

3.3 To have rapid, cheap and precise method to identify pathogens or chemical agents

3.4 Portable detection system

3.5 Mobile system for non-invasive unobtrusive and fast screening

3.6 To identify diseases caused by previously unknown pathogens and thus may be of use in rapidly choosing the most effective therapy

3.7 To interpret genome data using GIS

3.8 To detect and to classify microorganisms according to the volatile gases given off during metabolism (Electronic nose)

These results provided a valuable background to the discussions of the scenario meeting.

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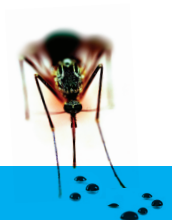

Chapter Two:
Planning, Technology & Life Cycle Framework

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Scenario Planning

Scenario planning is a way of envisaging what the future might hold for a particular economy, industry sector or organization for a period of 10-20 years ahead.[1-3] Rather than using projections from past trends as a forecast, scenario planning attempts to develop internally consistent stories about possible futures. It recognizes that the future is complex, uncertain and ambiguous. The essence of scenarios is that they: represent possible alternative futures; allow for qualitative perspectives; allow for discontinuities; allow us to develop new insights; enable us to express multiple views on complex events through stories; and enable us to develop strategies to deal with change.

The technique follows a series of steps. Using experts organised in breakout groups the key drivers of future change relevant to the study are identified. Then the uncertainties influencing these drivers are developed. Self-consistent scenarios are then constructed for an agreed time in the future. By working back (backcasting) from these pictures of the future, critical turning points can be identified which can be used to assist in policy decisions.

The Scenario Workshop

Thirty three experts from seven economies met in Thailand in February 2007 to develop scenarios for the future of EID in the Asia Pacific region. In order to develop the scenarios, participants identified key drivers[3] and uncertainties as follows:

Key Drivers for Emerging Infectious Diseases

Social

- Health concern for everyone
- Increasing population
- Urbanization
- Gap of knowledge sharing

Technology

- Complexity of transportation
- Nanotechnology
- Genetic modification
- Event tracking

Economics

- Free Trade Agreement
- Sufficient economy
- Rich poor gap

Environment

- Climate change
- Vector patterns changes
- Land use change
- Wild life – Changes of wild life consumption but pet trades will increase

Politics

- Terrorism
- Patent in developed countries, incubate for developing countries
- Wrong policy

Key Uncertainties for EIDs

- Massive natural disasters such as massive volcanoes, earthquakes, etc.
- Treat to global security (man-made disasters, alien species/ breakthrough tech.)
- Local/Global panic
- Urbanization: increase, Economic crisis
- Gap of knowledge sharing
- Unpredicted/unplanned technologies

Four scenarios for 2017 were then developed as:

Scenario 1 ***"Malaria in Miami 2017"***

In February 2015 a family arrives in Miami from tropical Latin America. A family member, a little girl, was infected with an unknown strain of Malaria. She had been bitten by carrier mosquitoes. There is no experience or history of treating this disease in Miami so disease spreads. Some deaths occur; no treatment is available and social unrest begins.

As the global carbon economy continues unchecked, global warming accelerates. Rising sea level creates "environment refugees" into Florida. Rainfall patterns change with Florida's climate becoming tropical. Inundation (flooding) of low lying land causes insect vectors to spread, more severe storms to occur and the hurricane season is extended, ultimately culminating in a category 5 hurricane hitting Miami on the New Year's Eve.

A human smuggling system develops to bring people from endemic drug-resistant malarial areas in Latin America through the Everglade swamps to Miami. Endemic malaria develops in swamps around Miami. A bad hurricane season leads to an increase in malaria – carrying mosquitoes. Sea levels rising push populations into swampy areas. Finally, a major category 5 hurricane destroys transportation and public services in Florida, loss of infrastructure – no mosquito control over many months. Drug-resistant malaria erupts in Miami. Food and water scarcity along with public violence disrupts access to care. Refugees are leaving infected region and carrying disease beyond Florida.

As the malaria pandemic progress, more children become infected and mortality rises. By 2017 the US Government is requested to take urgent action.

Scenario 2 *"20,000 People Now Confirmed Dead from Mystery Disease"*

Extract from Bangkok Post February 5, 2017.

Over the last 2 weeks, 20,000 people in Bangkok have been reported dead from a mystery disease and more than 50,000 sick. The resulting chaos has been the worst in the history of Thailand. Hospitals are overwhelmed with people claiming to be sick and doctors are overstressed dealing with patients at home. The economic consequences are severe with businesses unable to operate due to lack of staff while transport system are erratic and fuel supplies are limited. Tourism has plummeted and retailers are facing bankruptcy. Everyone is beginning to stockpile food, water and medicine.

Large numbers of birds have also been found dead throughout the city of Bangkok. Experts speculate that there could be a link to the dead ducks found in an intensive production facility located 50 Km away from Bangkok. Last month, at this facility about 1000 ducks died.

Disease investigation initially determined that the ducks were infected with duck plague. However, samples collected from dead birds in Bangkok were submitted to the National Institute of Animal Health and scientists have confirmed that these birds were infected with a novel flavi virus (transmitted by mosquitoes). Subsequently, testing of stored samples from the dead ducks confirmed that these were also infected with the same flavi virus.

Scientists have speculated that this flavi virus might have emerged in the large intensive duck production facility where genetically modified ducks had been specifically bred to be resistant to H5N1 virus. This breed of ducks might be particularly susceptible to flavi virus infection. At the time that breeding avian flu virus resistant ducks was first proposed, there was significant debate in the scientific and general community. Commercial pressure coupled with an overwhelming desire to avoid continuing H5N1 outbreaks finally convinced the government to approve the production of the genetically modified ducks.

Over the last 5 years, the city's population has been growing very rapidly. The water supply system has been stretched in recent years with the recent population growth. Last month, when the major water supply system failed, people started to store water for their households using a wide range of collection methods. The public health department had warned people to keep their water in covered storage to prevent the reproduction of mosquitoes. However, a large number of people ignored such warnings and it has been speculated that those new to the city kept water in jars even after the public water supply was restored.

The Royal Thai Government has declared a state of emergency and the armed forces are controlling population movement as people flee the city in panic. Education of schoolchildren is being continued by TV and a mosquito control program is underway. A spokesman said "we are confident that the situation is under control."

Scenario 3 *"Mysterious Death"*

At the third week of October 2017, "Mysterious death" was the headline news on television in almost every economy around the world. On a Larry King show, an APEC advisor was interviewed, where he explained that there are roughly 5,000 people being infected by the virus. Within this group there is 20% mortality, 60% are critically ill, 10-20% are recovering. The death rate is low because the disease is thermo- sensitive and only becomes virulent under hot climate. A real time International Press Conference via Holographic teleconference supported by IBM was held on 22 November 2017. Four scientists from France, Thailand, Canada and Chinese Taipei were interviewed and explained the research approach that they are working on to combat the disease.

It was revealed that the virus is called "Archaea virus". Origin of the virus is from animals in the Jurassic period. Due to severe global warming, the Greenland ice is melting and the Archaea virus has been brought back to life. Some animals particularly rodents carry the virus and have infected the local native population.

When expeditions returned from studying the soil and archaeology in Greenland, they carried the Jurassic virus from Greenland. There were no symptoms at the beginning but the virus mutated to human-human transmission. In a big International conference

on Biotechnology in Paris, the infected scientists spread the virus to their colleagues at the conference over dinner. The scientists then went home to various major cities and spread the disease. A pandemic soon happened.

A range of technologies was put to use to stop the virus. One year later at the Larry King show, the same scientists were interviewed. They revealed that the disease was now under control and vaccine was widely available to prevent its spread.

Scenario 4 *"Emerging Rainforest Syndrome (RFS)"*

Two response scenarios were envisaged by this breakout group.

Background

In 2009, an epidemic, with 600 dead and a mortality rate of 30%, occurred in 10 countries without knowing the cause. After tracing back to 2007, it was found that there had been a scientific meeting in a rainforest economy. At that time, there were 20 cases found of an unknown illness showing cold-like symptoms followed by flu-like symptoms such as chills and aches, followed by severe gastrointestinal distress, leading to death in 20% of the afflicted patients within 2 weeks. People who survived transmitted the disease, which was named Rainforest Syndrome in 2009.

A. RFS Contained

Scientists successfully isolated the disease pathogens in 2010 following the establishment of an international committee to combat rainforest syndrome (ICCRES) in 2009. The ICCRFS started to educate people and give recommendations as well as warnings. These included recommendations for avoiding development that disturbed the rainforest ecological system and brought people in contact with the yet-unidentified vectors. Vectors and reservoir involved in spreading to human (bats to intermediate rodents, then airborne) were also successfully isolated. In 2013, ICCRFS found an effective vaccine and antiviral and then established a vaccination policy in 2015. In 2017, there is a report showing zero cases in past 6 months investigation with a mortality rate of 3%.

B. RFS #1 Public Health Problem

Lack of information sharing led to an epidemiology study being delayed until 2011, with the result that more than 10,000 people died. While international meetings were held, no international committee was established and the recommendations of the meetings, which were voluntary to follow, were not heeded, so that the disease continued unabated. Technical measures were unsuccessful as well. The virus mutated so rapidly that even though one genotype was isolated, others increased in virulence.

There was no diagnostic, no antiviral, no vaccine and no measures to prevent people from contact with the vectors. The result was that in 2017, Rainforest Syndrome became the # 1 global public health problem.

Key Technology Domains and Applications

During the scenario development, experts were asked to use back-casting to identify key technological domains and potential technology applications that will intervene, prevent or reduce the impact of crisis in each scenario. Three technology domains and their technology applications were identified as follows:

Table 1: Key Technology Domains and Applications

Technology Domain	Technology Applications
Ubiquitous Computing	• Field tests networked • Data collection (real time) • Data mining • Mobile phone tracking • Data sharing • Modeling • Bioinformatics • Network system of countries signing up for info sharing
Treatment	• Drug design • Delivery vaccine • Vaccine development • Personalized medicine advance in pharmaceutics • Nano-delivery of drugs • Molecular medicine, Cell-based vaccine development advance in genetic engineering of virus and antiviral material • Conventional Drug Discovery
Diagnosis	• Micro/Nano array molecular • Implantable diagnostics • Simple thermographical scanner • Genotyping characterization • Advance in micro-fluidic device • Advance in genetic sequencing • Advance in lab on a chip

These were used as the basis of the technology roadmapping workshop in Japan.

An EID Life Cycle Model

Discussions in the scenario workshop identified an EID lifecycle model[4] (as shown in Figure 3), with four stages from preventive measures to surveillance and detection to treatment and prevention of spread.

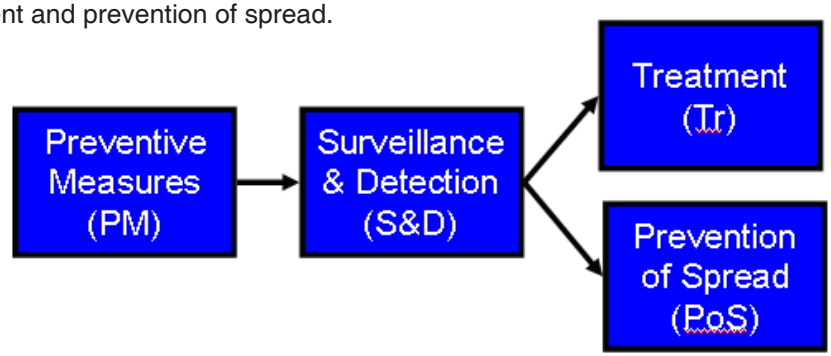

Figure 3: EID Life Cycle Model (adapted from RAND)

A key area of interest for this report is how technologies can converge to contribute to the overall capabilities for more effective EID management in the four designated lifecycle domains. Examples of these are:

1. Preventive measures (PM), which is the stage before emergence of EID. This covers technological approaches such as use of mosquito nets and insecticides in the case of malaria; future measures could include a preventive vaccine and new approaches to control the vector.
2. Surveillance & Detection (S&D) is the stage after emergence of EID. Current S&D includes diagnostic testing and monitoring of cases by person/place/time characteristics; future diagnostic or communication technologies could potentially improve upon the likelihood and timing of diagnosis and reporting.
3. Treatment (Tr), Current treatment options include drugs; future drugs could potentially be even more effective and cheaper.
4. Prevention of Spread (PoS), PoS include procedures to limit the transmission of the parasite, for example using tracking/monitoring.

The rest of this project employed this EID lifecycle model as the structure for discussions in the technology roadmapping workshops in both Japan and Chinese Taipei and the final symposium in Bangkok.

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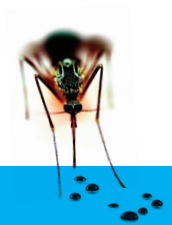

Chapter Three: Technology Roadmapping

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Introduction

"Roadmapping" and "Roadmap" are words describing the process and the product of roadmap development, respectively. Technology roadmapping is simply defined as an approach to portray the integration of science/technological considerations into product and business planning as well as to provide a way to identify, evaluate and select alternatives that can be used to achieve a desired objective.

Robert Galvin, former Motorola Chairman and advocate of science and technology roadmaps, said "A roadmap is an extended look at the future of a chosen field of inquiry composed from the collective knowledge and imagination of the brightest drivers of the change."[1]

Nowadays, technology roadmaps are widely used in industry, government and academia.[2-7] Their popular applications are for developing strategies, planning resources and identifying gaps and opportunities in R&D.[8-12]

The structure of roadmaps used in this study was designed by adapting from the generic format of a product/technology roadmap. The basic elements of a generic roadmap representing market, products, technology, R&D programs and resources, were changed into the elements as listed below:

- medical requirements of the targeted technology application used to combat EID
- development of technologies supporting the targeted technology application development, production & distribution and delivery
- key technical and policy challenges that could possibly hinder the progress of technology development
- R&D programs/activities required in delivering desired technologies

The timeframe of the roadmaps was divided into three periods: short term (2007-12), medium term (2012-2017) and long term (beyond 2017). The structure of roadmaps used in this study is shown in Figure 4.

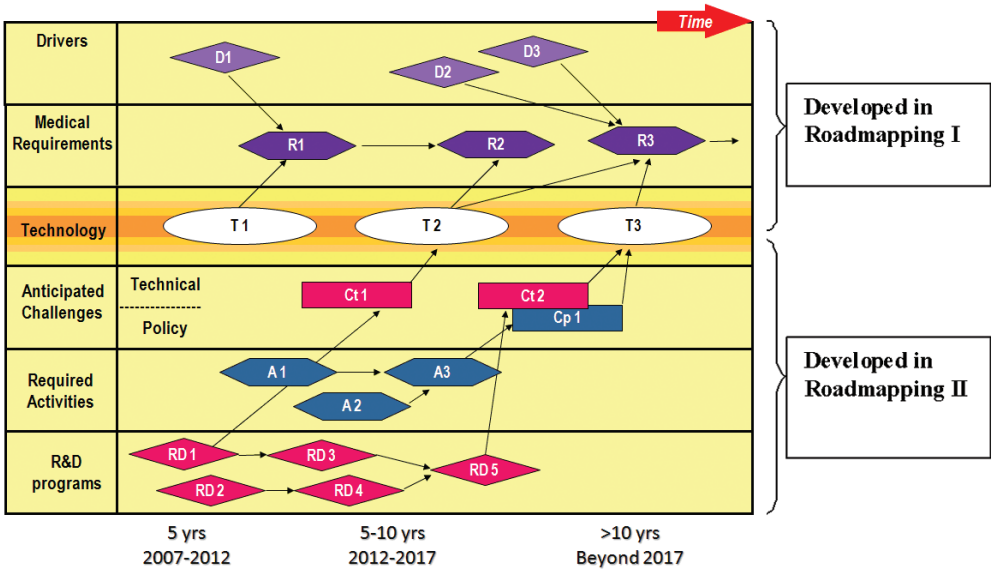

Figure 4: The roadmap structure developed in roadmapping session I&II

In this roadmap, drivers; D1, D2 and D3, are determined to be key forces driving the future changes of medical requirements in using the targeted technology application to deal with infectious diseases. These changes present as R1, R2 and R3 on the diagram. For example, D1 leads to the medical requirement; R1, which it can be supported by the use of existing technology; T1. Few years after that, the medical requirement; R1, is expected to be enhanced to the new stage which it is represented as R2 in the diagram. To respond to this new requirements; R2, the new technology; T2, needs to be developed. Ct1 is anticipated to be a key technical challenge hindering the development progress of T2. To overcome this challenge, an organization needs to invest in the R&D program; RD1. Following the same time horizon, new drivers; D2 and D3, are expected to gain more influent leading to the new medical requirement; R3. T2 will still be used in conjunction with the new technology; T3. A multi-stage R&D; RD1-5, needs to be planned to integrate these two technologies together. Also, a series of activities; A1-3, needs be organized in order to ease the key policy challenge; Cp1, in completing the development of T3.

The Roadmapping Workshops

To develop the roadmaps, two roadmapping workshops were organized in Japan and Chinese Taipei. The experts were asked to provide and share their views to the group on the following issues:

1. To determine the key trends presenting the changes of medical requirements on the uses of the targeted technology application for combating EID over the timeframe: short term (2007 - 2012), medium term (2012 - 2017) and long term (beyond 2017).
2. To identify key technology applications that can be utilized to respond to the needs as addressed in question 1 throughout the three periods
3. To define the scopes of technology applications including naming technologies for each technology application area within the three time frames.
4. To identify the technical and political challenges possibly hindering the development progress of key technologies.
5. To discuss the activities that should be exercised in order to overcome the technical and political challenges
6. To identify R&D programs supporting the development of key technologies

The first one in Japan in May 2007 brought together forty two experts representing nine APEC member economies to discuss the drivers, medical requirements guiding the development of technology applications in ubiquitous computing, treatments and diagnosis and technological/political challenges, including some activities across these challenges. The results were analyzed and presented as shown in Tables 2 and 3. During the workshop, experts also identified the technology domains of modeling, vaccines and tracking as having a high impact on combating EID.

The key user requirements for the three technology research domains were identified as shown in Table 2.

Table 2: Key User Requirements			
	User requirements Short term	***User requirements Medium term***	***User requirements Long term***
Ubiquitous Computing	• Information of EID • Fast detection of EID • EID preventing network system in Asia • IT for preventing social panic • Bio-terrorist alert system	• LAMP diagnostic equipment urgently needed for developing countries • Real time dynamics map/GIS • Animal protection • Border health security arrival gate • Realtime RFID health monitoring • Analysis of long time series land cover satellite data	• Forecast of possible hotspot • Smart dust health worker
Treatments	The need to improve • the development of existing drugs/ vaccines/ treatment to reduce side-effect • development of emergency vaccination program	• The need to develop effective drugs/ vaccine/ treatment which has the following characteristics: • Safe and zero side-effects • Use of new methods for drug design • Use of animal model for drug development • High throughput system	• The need to develop stable, long lasting, safe and affordable drugs/vaccine/ treatment with the following details: • Personalized medicine • Universal vaccine for influenza • Universal for strategy for structure-base drug design • Edible vaccine
Diagnosis	• Accuracy, No need to refrigerate • Long shelf life • Rapid test • Give result rapidly • Easy to use in the field • Small sample consumption • Reliability • Individual • Information for decision National • Sharing intellectual property and experience	• Individual • No physical Burden • Test without pain • EID education • Fast, no repetition • Cost • cheap • No physical burden	• Cost • cheap • No physical burden • Continuous microbial monitoring system

Recommendations related to the three technology research domains are listed in Table 3.

TABLE 3: TECHNOLOGY-RESEARCH RECOMMENDATIONS

	Recommendation Short term	***Recommendation Medium term***	***Recommendation Long term***
Ubiquitous Computing	• HRD: experts who can manage the epidemiological event /Training candidate who can participate epidemiological events • Education of community leader with "crude" surveillance technology tools • Warning system based on seasonal disease outbreak	• Supplying teacher (train the trainer) for sanitary education of EID • Regional alert & response network of EID • Predictive pandemic model (proactive based on many inputs + response) • Real time EID sharing information among different economies • Foundation of research center of public services in countries other than Japan/Korea/China	• Triage-knowledge should be educated to public • Predictive model of locating possible outbreaks • Network diagnostics for non-doctor
Treatments	• Need to have sufficient incentive to industries • Need to restructure trading regulation to support the exchange material and specimens across the border	• Network of APEC Center for clinical testing drugs • Need to prepare public to be aware of unknown future	• APEC vaccine production company • Educate people for GM materials
Diagnosis	• Improving database of genome, proteome of causative microbe • Need to have international/domestic system for sample delivery	• Research on Personal diagnostic devices • Need to solve problem on benefit sharing	• Research on field diagnostic devices • New light source for internal body scan • Visualization of pathogens • Detection method of infected cells

The second roadmapping workshop was organized in Chinese Taipei in October 2007. Forty one experts representing eight APEC member economies participated. The goal was to develop the three technology applications identified during the technology road mapping workshop in Japan.

They were: modeling, vaccines and tracking. These three technology applications seem to be unconnected. However, the discussions of the workshop revealed their inter-relationships and the role of technology convergence as the key to success in developing the technologies.

Development of the roadmaps resulted in the recommendations listed in Table 4.

Table 4: Roadmapping Recommendations

	Recommendation Short term	***Recommendation Medium term***	***Recommendation Long term***
Modeling	• Study climate changes and natural disaster impacts • Should have an EID 9/11 model • Need a CDC-WHO integrated approach • Need to work with e-sci industry	• EID model training for doctors • Global Models include social data + epidemic + economic risks • Global collaboration	• Strategies to confirm public acceptance respect and utility of models • Develop disease spread simulation • Economic impacts clearly identified • Simulate personalized/ genotyped response to unique genetic drugs Alignment with leading whole system models (health +security) • EID system standards for diverse model / action elements
Vaccines	• Chemical libraries exchange information • Support for patenting procedures • International coordination of human clinical trials • Research on detection and removal of contaminating material • Modeling for development of vaccine delivery system	• Set up core-lab available for state-of-the-art technologies • Risk assessment of GM organisms used for vaccine production	• Multidisciplinary collaboration between laboratories in material, data and information sharing
Tracking	• Government- funded wildlife capture and RFID tracking • Should have common system for collecting and analyzing data	• Establishment of standards/protocol for data sharing	• Need to track illegal immigrants • Develop specific enzyme or protein marker for EID

The six technology domains identified in the roadmapping workshops fit with the RAND model as shown in Figure 5. In keeping with the theme of converging technologies, there are links between all of the technology domains as shown earlier in Figure1.

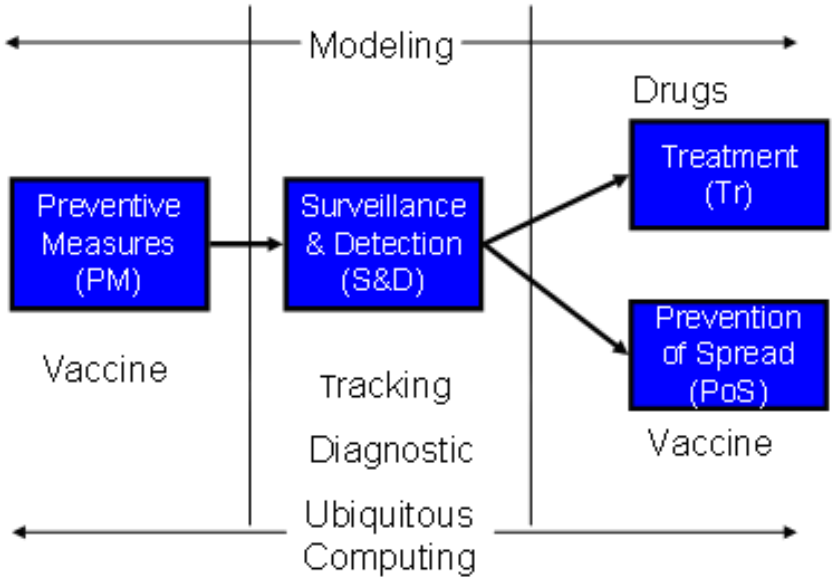

Figure 5: The contribution of technologies (using the RAND model) in combating EID

From the discussions in the roadmapping workshops and in the final symposium meeting, it was clear that there was a need to record more detail of each of the six domains identified as critical to the development of overall response strategies to outbreaks of emerging infectious diseases. To this end, a number of experts were invited to prepare short papers with descriptions of the domains leading to detailed roadmaps and recommendations.

The following chapters provide the coverage of the more detailed discussions which occurred during the roadmapping sessions.

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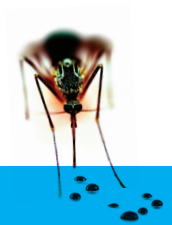

Chapter Four: Conclusion, Recommendations and Post-Foresight Activities

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The major conclusions of the study are:

- A life cycle model has been used to study the factors involved in initiation and spread of emerging infectious diseases namely, preventive measures, surveillance and detection and treatment and prevention of spread and to guide the development of responses in controlling these factors.
- This model can be linked to six significant technology domains namely, vaccines, diagnostics, ubiquitous computing, tracking, modeling and drugs. Each of these provides opportunities for converging technologies to make significant contributions to R&D and commercialization of devices and systems.
- Technology roadmaps have been developed for each of these domains to provide the basis for national and regional strategies for combating emerging infectious diseases.
- The significant findings for each of the domains are:
  - **Ubiquitous computing**-the concept of smarter information collection and management is an integral part of adoption of new processes and tools. Increased effort is needed to improve the automated analysis of surveillance data to enable early detection of outbreaks. Information technology is an integral part of developments in all the domains.
  - **Diagnostics**-a range of tools to enhance capability in these areas needs to be developed specifically for the Asia-Pacific region, particularly focused on low cost, portability and rapid information flow.
  - **Treatments**-more effort is needed on the development of therapeutic drugs for more effective risk management, even for those infectious diseases for which vaccines are available.
  - **Modeling**-availability of realistic models can assist policy makers in developing options for coping with out breaks but they cannot be used in real time when input data are changing rapidly.

- **Tracking-** miniaturized systems are being developed to track both animals and humans but standards and protocols are needed to enable tracking across national boundaries.
- **Vaccines-**vaccine development, production and delivery are essential components of any strategy to combat EID and must be strongly supported. New approaches based on genetic manipulation and molecular design will allow more rapid development of vaccines.

- The practical application of the concept of converging technologies in this project has created a new network of knowledgeable and concerned scientist and technologists in the APEC region. This can provide a focus for further co-operation.
- There is need for co-ordination of collaboration and sharing of information, facilities and training in combating EID across the APEC region. The APEC structure may provide a route to developing this co-ordination.
- The application of these new technologies in developing economies needs to be undertaken with great care, recognizing that there are major infrastructural, cultural and social differences. The "people factors" are crucial features of disease management through all phases of the life cycle model from detection to response.
- The translation of research outputs into policy is of critical importance. Politicians have to make decisions on the basis of available information which is often imperfect and hence the prompt and efficient transfer of information from the research environment into the policy environment is a critical component of effectively combating EID.

This project is a contribution to the better understanding of the provision of accelerated technological responses to combating EID in the APEC region and of the role of science and technology in providing those responses through the concept of converging technologies. However it is only a beginning and there is a need for further action by individual economies and by APEC itself as a co-ordination body to ensure that the region is adequately prepared for the outbreaks of emerging infectious diseases that will inevitably occur in the future.

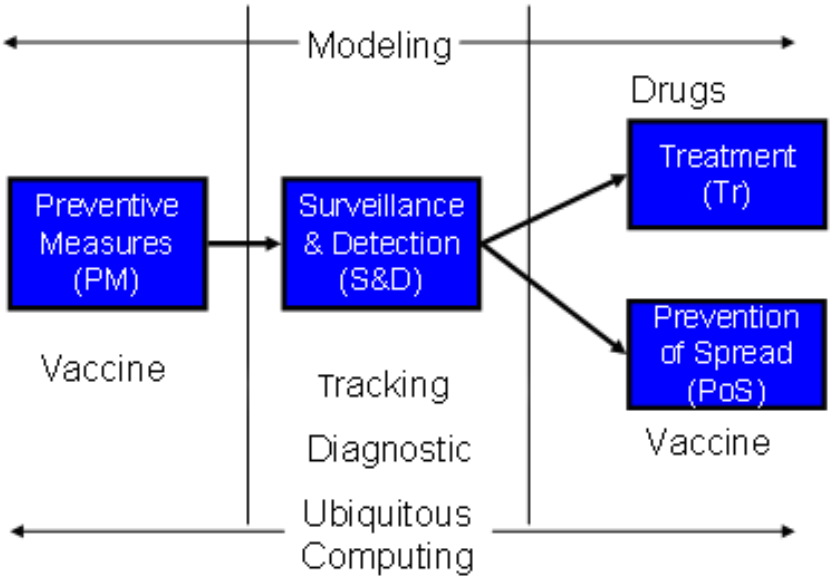
The increasing threat posed by emerging infectious diseases to the economic and social development of the APEC economies, as evidenced by the recent outbreaks of SARS and avian influenza, requires an accelerated technological response to prevent future disasters. It is clear from this project that the approach to combating emerging infectious diseases is changing rapidly as a result of the recognition that divergent technology domains must work together to a common goal. The concept of converging technologies can bring together and upgrade traditional disciplines through the application of nanotechnology, information technology and biotechnology and will become increasingly important in a number of fields.

An earlier APEC CTF project on "DNA Analysis for Human Health in the Post-Genomic Era" in 2003 concluded that the Foresight approach can be an effective mechanism

for handling complex issues involved in life sciences and this project has reinforced that conclusion. Thus the identification of the key technology domains of ubiquitous computing, treatment and diagnostic kits gained from the scenario creation workshop provided a valuable input to the later development of technology roadmaps. A further significant outcome of the scenario workshop was the identification of an EID life cycle model with four stages from preventive measures to surveillance to detection and treatment and prevention of spread. This model provided a framework for the project overall and provides a springboard for further studies.

The structure of the scenario and the technology roadmapping workshops enabled experts from a variety of disciplines and viewpoints to work together to apply their skills in nanotechnology, genomics, bioinformatics, communication technology, biotechnology, modeling and risk management, vaccines etc to a common problem. Such a diverse group would never normally meet together to exchange information and to look for synergies between their areas of interest. A new network of knowledgeable and concerned scientists and technologists has been created in the APEC region as a result of this project. This needs to maintained and developed as part of the activities in APEC.

Significant conclusions and recommendations of the project in terms of the EID life cycle model of Figure 5 (page 35) are:



Preventive Measures

- Vaccine development, production and delivery are essential components of any strategy to combat EID and must be strongly supported.
- While current techniques are relatively slow, advances in genome manipulation and molecular design will allow more rapid development of vaccines to meet new threats. These developments must be pursued as rapidly as practicable.
- Vaccine production is currently limited to a small number of countries but these developments from converging technologies may allow more rapid transfer of new vaccine production to developing countries.
- Effective delivery of vaccines by mass vaccination techniques is critical to successful prevention of EID. New delivery systems should be studied.
- In maintaining immunisation it is essential to have continuous upgrading as drug resistant strains develop and potency decreases.
- Disease data warehouse should be built and effort to apply data mining analysis for EID should be given with the purpose to reveal early warning signs.

Surveillance and Detection

- Many countries in the region have made substantial improvements to their disease surveillance and information collection capacity through web-based information collection systems since the SARS 2002 outbreak. However information flow from rural areas remains a significant challenge and needs attention.
- Tracking systems are becoming more sophisticated with miniaturised tagging systems being developed to track both animals and humans. Since 70 per cent of EID are of animal origin, standardisation of systems is essential to allow tracking across national boundaries.
- There has been rapid progress in developing technologies for multiplex testing and point-of-care testing but they need to be applied in controlled environments. The application of new reagents has the potential to revolutionise testing for the presence of micro-organisms. The common need for developing countries is cheap, reliable tests for use in the field.
- While the converging technologies approach has resulted in major advances in genomics and informatics applied to diagnosis there are now problems in handling the very large amounts of data that can be produced and new approaches are needed.
- The importance of information management becomes apparent when considering the very large amounts of diagnostic data coupled to surveillance data. The crucial element is to connect data sets at high level, to improve the way in which data sets are shared and the ways in which they are analyzed. The cost of automated equipment to deal with these data is beyond the budgets of many developing countries and ways need to be sought to reduce costs..

- Modeling is one way in which data can be used to inform policy and assist in better decision making since modeling provides options and advice. However this must be done prior to any outbreak and cannot be used in real time when input data are changing rapidly. It can be of great value in training.

Treatment and Prevention of Spread

- Past experience shows that even for those infectious diseases for which preventive vaccine is available, therapeutic drugs are required for more effective risk management.
- Development of drugs which inhibit replication or pathogenic mechanisms of the lethal micro-organisms is an urgent challenge. Structural analysis of pathogen molecules needs to be accelerated to enable effective drug design.
- Genomic-based molecular modeling offers new opportunities for drug design but markets are limited and new business models are needed for commercialisation.
- Rapid development and mass delivery of vaccines based on viral strains collected at early stages of epidemics is needed since the epidemic strain may be a mutant one.
- As in immunisation, the effective use of vaccines for prevention of spread requires continuous upgrading as drug resistant strains develop and potency decreases.
- Computing capacity and model complexity will have potential to speed up and reduce waste of trial in drugs or vaccine development process.
- Epidemic forecasting model will enhance the effectiveness for planning operations. The priority is now to incorporate geographical and climate data with the disease knowledge of disease spread into model construction. Lifestyle, social and economic factors will be continuously added on.

A number of more general conclusions and recommendations arise from the discussions of the workshops, namely:

- There are large differences between and within, APEC economies in their capabilities to understand, let alone, develop many of the technologies needed for an integrated approach to combating EID. The approach of converging technologies may be possible in developed and larger developing economies but the cost of equipment is still expected to be too expensive in the short-term. A major challenge noted in several cases above is to accelerate the development of cheaper and cost-efficient tracking, diagnostic testing and sequencing technology to ensure broad equity across APEC economies.
- A significant area is the co-ordination of collaboration and sharing of information, facilities and training across APEC to redress the imbalances amongst economies. One model for collaboration based on Japanese experience in developing countries in Asia and Africa is described in the Post Foresight RIKEN contribution by Dr Okamoto. This could form the basis for an APEC approach and needs to be studied.

- The rapid increase in zoonic diseases, i.e. diseases transmitted from animals to humans, seems certain to continue as populations of large cities increase in Asia and humans and domestic animals interact more closely, coupled with the move to bring more virgin forest and jungle under cultivation thus increasing contact with wild animals. The concept of converging technologies then becomes more important to ensure that experts in human and animal health and diseases work together more closely.
- The application of these new technologies in developing economies needs to be undertaken with great care, recognising the infrastructure, cultural and behavioural issues. The “people factors” remain crucial features of disease management. Thus participatory disease control, education and building & maintaining networks play an important part in disease control. The inputs from people in the field are as vital as is their response to outbreaks.
- The translation of research outputs into policy is of critical importance. Scientists and the public have different perceptions on information and risk. Politicians and the public need a better understanding of complexity and uncertainty. Scientists need to understand that politicians have to make decisions in the absence of all the required information and when all the risk factors may not always be apparent, hence, the prompt and efficient transfer of information from the research environment into the policy environment is a critical component of effectively combating the emergence and spread of emerging infectious diseases.

In summary, table 5 illustrates crucial technological requirements to combat EID and technology applications needed to response to these requirements. The technological requirements were categorized into four phase of EID lifecycle model where the technology applications were grouped into the six technology domains suggested and discussed in the technology roadmapping workshops in Japan and Chinese Taipei.

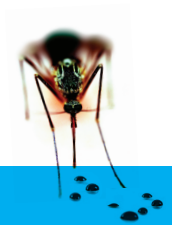
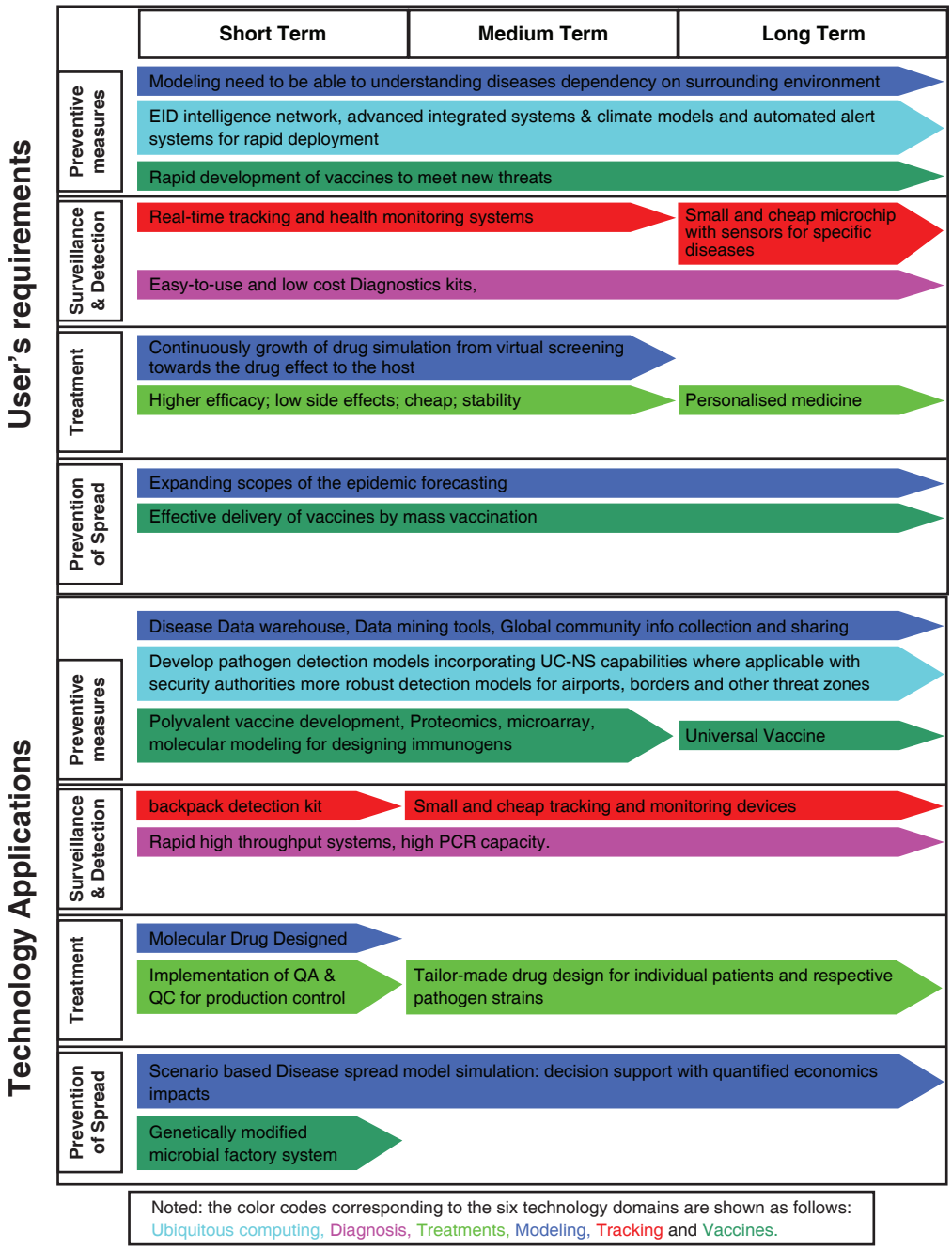


Table 5: Integrated roadmap of converging technologies to combat EID



Noted: the color codes corresponding to the six technology domains are shown as follows: Ubiquitous computing, Diagnosis, Treatments, Modeling, Tracking and Vaccines.

Table 6: Summary of Technology-Research Recommendations			
	Recommendation Short Term	***Recommendation Medium Term***	***Recommendation Long Term***
Ubiquitous Computing	• HRD: experts who can manage the epidemiological event /Training candidate who can participate epidemiological events • Education of community leader with "crude" surveillance technology tools • Warning system based on seasonal disease outbreak	• Supplying teacher (train the trainer) for sanitary education of EID • Regional alert & response network of EID • Predictive pandemic model (proactive based on many inputs + response) • Real time EID sharing information among different economies • Foundation of research center of public services in countries other than Japan/ Korea/China	• Triage-knowledge should be educated to public • Predictive model of locating possible outbreaks • Network diagnostics for non-doctor
Treatments	• Need to have sufficient incentive to industries • Need to restructure trading regulation to support the exchange material and specimens across the border	• Network of APEC Center for clinical testing drugs • Need to prepare public to be aware of unknown future	• APEC vaccine production company • Educate people for GM materials
Diagnosis	• Improving database of genome, proteome of causative microbe • Need to have international/domestic system for sample delivery	• Research on Personal diagnostic devices • Need to solve problem on benefit sharing	• Research on field diagnostic devices • New light source for internal scan • Visualization of pathogens • Detection method of infected cells

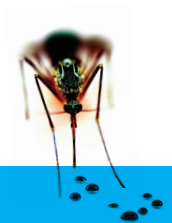


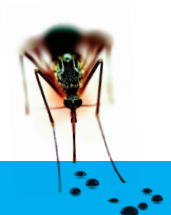
Table 7: Summary of Roadmapping Recommendations			
	Recommendation Short Term	***Recommendation Medium Term***	***Recommendation Long Term***
Modeling	• Building ICT platform and standards trajectory to enable data and resource sharing and interoperability • Program for cross discipline HR collaboration to combat EID • R&D funding program for e-science connection focus on converging technologies with focus in attacking EID	• Development of global-regional technology exchanges for EID simulation-modeling • Investment in VR/serious cyber gaming as virtual lab to understand EID threats and impacts in scenario based modeling • Develop more sophisticate climate and land use impact model	• Adoption of effective computational model into process management
Vaccines	• Chemical libraries exchange information • Support for patenting procedures • International coordination of human clinical trials • Research on detection and removal of contaminating material • Modeling for development of vaccine delivery system	• Set up core-lab available for state-of-the-art technologies • Risk assessment of GM organisms used for vaccine production	• Multidisciplinary collaboration between laboratories in material, data and information sharing
Animal tracking	• Government- funded wildlife capture and RFID tracking • Should have common system for collecting and analyzing data	• Establishment of standards/protocol for data sharing	• Need to track illegal immigrants • Develop specific enzyme or protein marker for EID

Post-Foresight Activities

With strong user inputs in scientific and management issues, the foresight project appears to have high potential to inspire and influence decision-making regarding EID throughout the Asia-Pacific region. Such a continuity of effort to disseminate the outputs of the project and inspire other activities during the later stages of the project and after its termination is usually called “Post-Foresight Activities”.

In this project, many fruitful discussions occurred during this two year project. These suggested potential activities that could have a high impact in efforts to combat EID. A number of the activities related to the foresight project were initiated during and after the project ended. For example:

- It has been pointed out several times that APEC developing economies are often lack of financial resources and health service infrastructures to support combating EID. Budget allocation, selection of R&D and selection of existing interventions for implementation are critical problems. These issues were included in the ‘challenges’ part in every roadmap.
- RAND Corporation, who participated in the key events of the project, has proposed a decision model to identify and evaluate an optimum mix of interventions and measures for a specific disease as improvements in health infrastructure, which can concurrently benefit more than just a single disease. The model will take into account the existing situation on the ground, evidence-based metrics of coverage and efficacy, financial requirements and the intended time horizon. The proposal is being considered by the Global fund for funding, with potential involvement of the APEC Center for Technology Foresight and its partnering scientists. It is hoped that eventually the outcome of this project will assist developing APEC member economies in order to optimize the research budget and set policy directions in an effective manner. *Proposing Institution: RAND Corporation, USA.*
- A discussion which developed mainly in the diagnosis roadmap suggested a new network system could be based on a fully scientific base and this should be established as a research and diagnosis center of infectious diseases among APEC economies. This proposed center could be used as a hub of the network, with samples, information and human resources shared by Asian countries. Currently, RIKEN, the leading governmental research institute of Japan, is developing laboratories in collaboration with Thailand, Viet Nam, China, Indonesia, India, Philippines, Zambia and Ghana. Subsequently, Dr Okamoto from RIKEN, who was a key contributor to the foresight project, also addressed the possibility of using one of the RIKEN research bases as an APEC diagnosis center, combining with establishment of a new network system to utilize other research sites effectively for the benefit of the APEC. In order to make significant progress in combating EID, sharing of samples, people and information will be highly required. Therefore, this initiative could provide a great benefit among APEC member economies as it would



establish strong partnerships within APEC and also could enable African research organizations and researchers to study or analyze local samples collaboratively. *Proposing Institution: RIKEN, Japan.*

- It was stressed in the meetings/workshops of the project that in order to make the best use of the foresight roadmaps, the results should be disseminated to a broad range of (and certainly to those in positions of authority) stakeholders. In Thailand, M.D. Ram Rangsin, a Thai medical expert, has been conducting a project on developing policy recommendations of EID surveillance system for the Thai government. The findings from this APEC-wide project were shared and information was provided to this surveillance project especially with respect to the technological trends and policy recommendations of technologies in ubiquitous computing, modeling and disease tracking.

In summary, the prospect is good that the findings from this foresight and roadmapping can be integrated as policy recommendations in key APEC economies ready to action them.

Part II: Roadmaps

Chapter Five: Ubiquitous Computing-Network Systems (UC-NS)

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Introduction to UC-NS

As the world of interlocking networks has evolved through the Internet and its gradual migration toward data driven communications between servers and node elements, the vision of a world in which sharing of information is both effortless and ubiquitous becomes more accessible. In the late 1980s, XEROX PARC under the leadership of Mark Weiser[1] began to call this vision Ubiquitous Computing. Subsequent work has expanded the description of an ability to maintain continuous connection through time and space as ambient intelligence[2].

> *Ubiquitous computing names the third wave in computing, which is just now beginning. The first wave included mainframes, each shared by lots of people. Now we are in the personal computing era, person and machine staring uneasily at each other across the desktop. Next comes ubiquitous computing, or the age of calm technology, when technology recedes into the background of our lives. Alan Kay, formerly of Apple, calls this "Third Paradigm" computing.*
>
> *Ubiquitous computing is roughly the opposite of virtual reality. Where virtual reality puts people inside a computer-generated world, ubiquitous computing forces the computer to live out here in the world with people. Virtual reality is primarily a horse power problem; ubiquitous computing is a very difficult integration of human factors, computer science, engineering, and social sciences.*

The capacity being developed is to construct ICT systems that recognize users. These systems are widely- even pervasively available at all times and like writing and signage. They are so familiar that they fade into the background and are assumed to be always capable of aiding, accessing and guiding individuals and their knowledge to connect with designated others.

Such systems rely on highly robust and richly embedded sensors and network connected nodes that are essentially able to make any surface, object or person a mode of connection and knowledge capacity within as highly "sensor-ized" system. By

connecting inanimate objects with each other and providing information capacity to and from the network, ambient intelligence enables large numbers of dumb objects to be joined to create smart systems capable of certain rudimentary, but important functions such as user recognition, connection and ambient sensing.

What is particularly intriguing for the deployment of these unique new systems, whether in security, ecological monitoring or health applications, is the extent of interplay, interdependence and the multidisciplinary approaches required for the knowledge capture and interpretation between the human behaviour requirements and the presence and performance of physical components such as molecular level detection sensors, or signalling devices.

In the context of the future detection, mitigation and management of emerging infectious diseases, the enabled communication and computation capacities of these systems become very important for all stages of preparedness and effective response to disease.

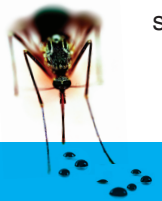
Emerging Infectious Diseases and UC-NS

As interconnected systems have evolved into GRIDs, Mesh Networks, E Platforms and other forms of highly connected and computational capable infrastructures, such as those envisioned within the descriptions of UC-NS, both the architecture and the hardware elements have advanced, sometimes quite rapidly because of their strong links to mobile networks deployment.

The APEC EID Technology Roadmap process investigated how many of these prospective developments could eventually be harnessed to significantly improve our capacities for detection, mitigation and management of EID. This process of linking ubiquitous computing developments to disease tracking and diagnosis has evolved rapidly, with international conferences now devoted to the subject and including leading academics and health care professionals.[3]

The initial step in the process was to unleash the imaginative capacities of a highly skilled set of public health and science and technology experts by challenging them to create future plausible scenarios in which advanced computational abilities would be available to professionals called upon to contain and manage pandemic intensity level disease threats. From the four scenarios that were created, an initial set of parameters was identified that was useful in guiding the subsequent analysis of barriers and potentials for UC-NS in EID alerts and management. These included the following elements:

- Use of distributed real time data sets on disease characteristics to conduct instantaneous networked field tests and simulations against known disease symptoms-characteristics;



- Data mining to connect disease vectors with possible sources and spread variables that will need to be considered for containment, diagnostics and treatment;
- Mobile phone and other devices tracking in geo-space-time and linked to modeling abilities;
- Bioinformatics data integration into the EID system and its international connections;
- At source level alert-detection using UC-INS sensors;
- Linkages with land use, climate models and human behavior - network spread models for enhanced prediction of disease emergence and spread patterns.

This list then became the starting point for a technology roadmapping process that was designed to deepen our prospective views on how UC-NS might evolve in the future as a key technology for EID management. The second phase of the work was undertaken in Japan where a breakout group of experts examined the 5, 10 and 15 year horizons for the evolution of ubiquitous computing in the context of EID. The following charts and tables summarize the discussions of this group.

Table 8: User Requirements & Technology Needs for EID & UC-NS in the Asia-Pacific Region

Short Term: 2008-2011	*Medium Term: 2012-2016*	*Long Term: 2017-2020*
User Requirements for EID Application – (**bold** areas identify those requirements central to UC-NS technology) *Note: the UC Expert Group started by discussing general user requirements and gradually focused more on the technology horizons for UC-NS*		
• Provide Statistics data of diseases • Document present status of ICT capability of APEC economies • Identification of climatic indicators • Keep Healthy (social) network • Promote culture of sharing information, collecting data • Reinforce alert systems to prevent hospital infection (nosocomial infection) • Increase EID education in schools, TV and Mass media • Automate available information and develop symptom checklist • Create diagnostics and treatment model to be available on internet (Google-Meds) like on-line AI-consultant • Produce/educate ICT+ public health experts • Link public health network to core group of scientists & researchers + ICT networks • Design ICT solutions that make people at ease, not panic, chaos • Digitize and web post most recent information of EID: i.e. Infection pathways; Treatment methods; animals • Disease Confirmation Test kit • Characterize Pathogen • Develop new methods for fast detection • Design systems for airport station detection • EID preventing network system in Asia • IT for preventing social panic • Bio-terrorist alert system tied into surveillance • Consider how to manage databases of affected patients • Immediate sensing of disease/ pathogen presence	• Monitoring EID prevention • Social Support: e.g. (Free) Hospital Financial support system; and Government support for innovation in health, ICT system • Avatar for informing professionals of disease/health alerts • Mechanism for identification of infected vector • Digital model diagnostic equipment urgently needed for developing countries • Real Time (network spread) dynamics/contact maps/GIS • Animal protection (stop culling birds/pigs/cows) • Border/airport health security arrival gate (smart sensor) • Portable Lab on chip for rapid full diagnostics of samples • Model for application and drugs effectiveness • Real time RFID Health monitoring (Bio+nano) • Supporting ICT infrastructure • Analysis of long-time series land cover satellite data	• Forecast of possible probable hotspot (Forecasting model) • Stronger human immune to EID • Smart dust (tracking people) health worker • EID traceability system with ubiquitous device • Micro RFID markers tagging for wild birds migration pattern • Grid computing / network of distributed computing (like earth simulator) • Early warning and modeling of disease outbreak • Advanced Voice Emerging Response Technology • Pod-casting resource (similar concept to push mail /RSS) on reliable network – push web • Integrated alert systems to detect emerging disease (for airport) = smart sensor • Push mail (alert system for key worker) • RFID tagging to wild animals (trace transmitting route) • Wiki-Google-office-like workspace tools for EID KM /web portals/ Very Small Aperture Terminal (VSAT) for communication • 3G technologies for diagnosis/ reporting • Regional spatial database for EID • Emergency Call System before going to Hospital, to avoid diffusion, when suspicious (social factor considered)

As of 2008, the shape and potential for the eventual infrastructure of the UC-NS still remains somewhat elusive - still more imagined than accessible - since EID leaders are still waiting for several key innovations to be confirmed and implemented.

The Japan TRM meeting also examined some of the obstacles that moving toward UC-NS will entail and it identified those factors that are encouraging the necessary innovations. The following tables identify both the strategic and operational barriers that will need to be overcome and the technical and other change drivers which are relentlessly pushing these developments forward.

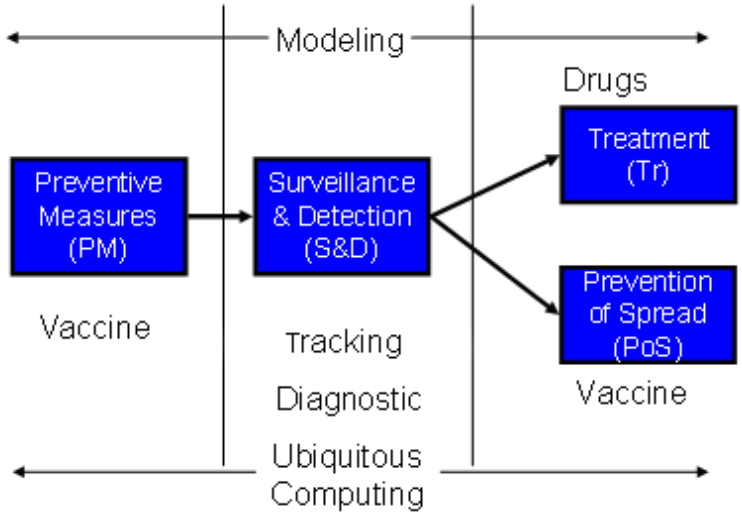
Table 9: Barriers for UC-NS Development

Barrier Type	*Short Term*	*Medium Term*	*Long Term*
Socio-economic: energy costs rising faster than computation returns-benefits to most economies (crises potential)	UC-NS is energy intensive and still relatively costly	Renewable sources and new server architectures that are designed to save energy should increase UC-NS.	The energy factor could eventually become an asset for UC-NS as energy becomes fully computationally delivered and its use is efficiently managed
Technology: IPV6: take up and acceptance is encountering mixed results, slower adoption rates	Global economic cleavages persist, slowing the transitions required.	IPV6 will eventually acquire adequate support or be supplanted by a more powerful standard.	Long term view is for IPV8-10 with significantly increased fit with evolving UC-AIS requirements
Technology: device integration and seamless interfaces are slow because of deference to hardware innovators	Outlook for the short term is for more of the same.	New devices can be expected which will have connectivity more easily built into them and able to benefit from high levels of processing power and increased storage capacities.	Standards for UC-NS should be in place which can ensure device integration will no longer be the major barrier it now represents.
Governments: pre-occupied by immediate security and socio-economic dislocations	The business cycle and more immediate pressures are working to divert previously promised investments	Question ensures about whether investing in technology versus people is still a key choice for senior managers.	Governments are no longer the leaders they once were, so focus is on the larger LT opportunity as the 21st century evolves toward the "Singularity"[4]

Socio-economic: Lack of industry demand and/or government coordination on standards for UC-AINS	Many APEC economies continue to lack the strong stakeholders needed for fast development.	Collaborative development will likely be essential to accelerate the innovation demand function.	UC-NS will more likely be driven by commercial and security markets than by technology push from government health related sources.
Governments: gradual complacency regarding security Threats, results in lower priority for infrastructure upgrades	Complexity of infrastructure re-development plus the urgency of security upgrades has receded – i.e. public investment responds to current crises.	UC-NS will more likely follow the general pattern of infrastructure renewal- i.e. gradual implementation.	There remain major uncertainties about when and how the UC-NS infrastructure will emerge.
Socio-economic: global traceability being held back by privacy and global competitive forces	In the short term, privacy issues loom high as a barrier.	For the medium term privacy issues will likely be subject to renewed scrutiny; -critical determinants will be either to access commerce or the urgency of national security.	EID will not likely be the tipping point for UC-NS deployment unless a major pandemic recurs with substantial impacts.
Governments: EID and educational networks for front line personnel are not being adequately funded to enable UC-NS development	As above, EID alone is not seen as the determining driver for UC-NS.	The computational horizon will likely follow paradigm shifts in commerce and security as noted elsewhere.	In the long term, the shift may require generation change.

Roles of UC-NS in Combating EID

A key area of interest for this report is how each of the converging technology categories is contributing to the overall capabilities for more effective EID management in the four designated priority EID lifecycle (RAND) domains:



As the diagram (Figure 5 from page 35) indicates, ubiquitous computing and modeling have broad applications across the full scope of the four domains of the life cycle. This has the effect of tying the development of UC-NS to those drivers having the force of change in any one, or more frequently all, of the domains. This is consistent with the future of UC-NS as a new infrastructure for managing all of these domains as they evolve toward a greater dependency on computation, mobile data sources and virtuality-simulation as a way of assessing risk, identifying the magnitude of threat and dimensioning responses.

In the short to medium term, advanced ubiquitous computing is most likely to occur in disease tracking and monitoring through increased power of the networks capacities for surveillance and detection.[5] The EID lifecycle model is useful for demonstrating that to be truly applicable to the challenges associated with EID, all four stages of the life cycle will eventually have to be engaged.

Of particular interest for this chapter is that UC-NS, according to the RAND model, should be broadly viewed as a full lifecycle technology that will underpin all functions eventually once it reaches a level of maturation that the barriers identified above are now delaying and inhibiting.

As these barriers begin to be addressed going forward from 2008, there are strong drivers for change that portend many new potentials and capabilities that EID strategists can begin to both imagine and develop. These drivers are formidable insofar as they relate less to the technologies for UC-NS themselves than to the context of how EID is positioned within the evolving socio-economic fabric of the region and its aspirations to overcome the pandemic risks that have periodically threatened the economic vitality of many of the largest populations in the region.

Table 10: represents how these drivers can provide the impetus for such changes:

Table 10: Technical and Other Drivers of UC-NS Development to Combat EID in the Asia-Pacific Region	
Change Driver	***Description-Impact***
1. Global response to SARS-HVN1	Massive increase in technology development and deployment = major boost to UC-NS
2. Cost of pandemics to economy	Cost-effectiveness of UC-NS measures now can be evaluated more readily
3. Recognition of one health world+ shared animal-human health	Greater international collaboration on how UC-NS might be applied to EID
4. Exponential increase in mobility-travel and mixing of populations	UC-NS may be a key tool for predictive impacts of this driver in the future once key data tracking elements are available
5. Complexity increases due to changes to land use, climate, global warming impacts	Linking UC-NS data to modeling- simulation may enable new understanding of how these changes impact disease origins, spreading, endurance and eradication
6. New zoonotic & viral diseases require early characterization	UC-NS may aid characterization by supplying key context data, mobility factors for animals and other zoonotic sources
7. Integration of complex detection systems combining mobile, fixed, virtual sources & elements	UC-NS is premised upon new ways of integrating diversely sourced data, devices and application modes – as these grow so will UC
8. Global safety and physical security- anti-terrorist measures	While this driver may wax and wane with the perceived level of insecurity, it represents a major source of R&D and a test bed for UC-NS early adoption measures
9. Move to traceability systems for complexity management	Eco-environmental systems are moving toward cradle-grave traceability and UC-NS technologies could find these applications become killer applications before more privacy related ones are widely accepted
10. Massive increase in computational speeds, storage, infrastructure	UC-NS really is a new stage or paradigm for computation and it will take off when the other demand and support elements begin to be realizable on a large scale
11. Singularity progress toward new paradigms for machine-bio intelligence integration	Kurzweil[6] presents a challenging vision of how the space between computers as machine based intelligence and humans as biological intelligence will dramatically narrow - UC-NS is an integral component of this vision
12. Breakthroughs in computational systems- nano and quantum devices	Progress continues to be made on these prospects at places such as the Institute for Quantum Computing at the University of Waterloo in Canada[1]. UC-NS may ultimately depend upon such breakthroughs

Roadmap Discussion

As a technology roadmapping collaboration, this project focused on the process for integrating knowledge and identifying future technology prospects and needs in several advanced domains that have been described together as UC-NS. These form a key part of larger systems integration that we have termed Converging Technologies because of their interdependent and symbiotic characteristics.

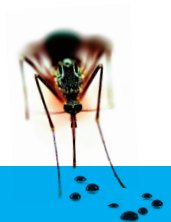
For the application of UC-NS to the challenges of EID in the Asia-Pacific region, several key messages, conclusions and policy recommendations for APEC are derived from the expert consultations and meetings in Phang Nga, Tokyo, Taipei and Bangkok respectively during 2007.

Distillation of these meetings produces some critical opportunities and ways forward so that the APEC region can become a global leader in the development, adoption and deployment of UC-NS against the challenges of EID which remain a persistent and imminent threat.

Table 11: Technology roadmap for UC-NS.

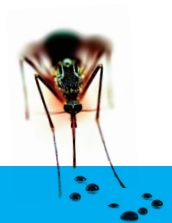
Table 11: Technology Roadmap Synthesis for EID & UC-NS Development in the Asia-Pacific Region		
Short Term: 2008 - 2011	***Medium Term: 2012 - 2016***	***Long Term: 2017 - 2020***
User Requirements for EID Application		
• Design architecture for broadly based, expert networks focused on rapid alert and mobile data acquisition • Development of databases, web interfaces and public alert systems that avoid panic response.	• Higher data capacity tools • Managed EID intelligence network and automated alert systems for rapid deployment • Initial border point data systems • Diagnostic models and avatars for health professionals to better manage the flood of new information being generated by early UC-NS	• Seamless, distributed real time expert response plus ambient networks capacity for rapid characterization and containment of EID and collaborative • Deployment strategies using advanced integrated systems & climate models - including smart nano-bio-info sensors, voice recognition, traceability systems • Widespread use of RFID tracking of target disease carriers.

Challenges & Barriers: (Technical, Political, Economic)		
• High energy and other costs for initial development • Fragmented device and software providers markets • Governments preoccupied by security and economic dislocations • IPV6 adoption and funding for digital infrastructure standards – to be able to accelerate EID applications.	• Educating the public remains a key task especially given the tendency toward EID complacency • No standards for UC-NS development or procurement • Infrastructure upgrading remains a low priority for most governments • IPV6 is slowly being adopted, but UC-NS is not seeing much development • Cost of sensors manufacture and systems for extracting data and managing pattern recognition still represent adoption barriers for UC-NS	• Speed, storage and volume issues related to what UC-NS requires for seamless deployment should be solved by 2020 • There may remain issues of personal data privacy, authenticity and identity validation that continue to stall the deployment of UC-NS • The defense and security world will likely lead the procurement of UC-NS, followed by leading edge commercial providers of personal enhancement systems – these can both support EID applications and divert attention from the health domain • Developing seamless systems will be more difficult than expected because of the different economic and technical abilities throughout the Asia-Pacific region
Technology Strategies for UC-NS Development & Deployment (Top Five)		
• Strengthen security-border screening systems by adding EID features where possible • Develop pathogen detection models incorporating UC-NS capabilities where applicable • Integrate climate and land use models into EID regarding and UC-NS design innovations • Work to accelerate IPV6 adoption plus support EID applications • Work with mobile wireless device producers to find a cheap in field device for disease alerts input data	• Further the development of electronic nose technology applied to EID management • Develop, with security authorities more robust detection models for airports, borders and other threat zones • Continue to support integration of nano-bio innovations into EID systems • Refine training models and focused programs for EID personnel • Predictive pandemics model with sensors ready to monitor developments and spread factors.	• Develop strong public health-alerts in which leading edge technologies and UC-NS elements feature prominently • Monitor Singularity progress and adjust models and detection-alerts-response systems • Develop test beds for UC-NS applications, integrated with climate and land use-human behaviour models; • Incorporate nanotechnology applications into EID toolkits and alert systems: e.g. smart dust • Deploy widely EID sensors as part of UC-NS innovation systems development and demonstration: e.g. lab on a chip linked to mobile phones; advanced voice data systems, next generation micro RFID tags.



EID Follow Up: Activities and R&D Programs		
• Continue to promote EID networks such as the IDRC project • Develop the E Science connections that will be critical for the next generation of UC-NS systems • Use existing R&D into global health to build a basis for stronger EID models and rapid characterization • Monitor impacts of climate change and land use regarding EID patterns – and key predictive factors • Build relationships with security-border agencies regarding disease technology futures • Advocate stronger web presence for EID fighting agencies and networks	• Fast pathogen detection using smart models and UC-NS data if available • Implement EID-UC-NS training programs • Incorporate genetic models into tracking systems • Implement more sophisticated climate and land use impact models • Bio-substance monitors integrated with expert systems software • Smart clothing with built-in disinfectant and sensors linked to treatment centers for early alert frontlines • Data mining and UC-NS ready system elements • Continued development of global-regional state-of-the-art technology and simulation-modeling exchanges for EID management	• Integrate new computational architectures, devices – e.g quantum • Incorporate new innovations such as nano-in vitro devices into EID UC-NS tools • Integrate new biomaterials – biocidals, anti-virals • Employ serious games, Second Life etc, to better understand EID threat factors in a UC-NS context • Practice preparedness via simulated viral attacks, new pathogens etc. • Examine how developments in virtual reality, holography and info-based 3D physical development might improve EID management • Genotype public response models and scenarios for managing EID future crises • Geo-strategic integrated data systems like weather reports for EID daily status – and spread dynamics

Table 12: Key Pplicy Recommendations for APEC Regarding UC-NS Development and Expected Impacts			
Policy Recommendation	***Short Term: 2008 - 2011***	***Medium Term: 2012 - 2016***	***Long Term: 2017 - 2020***
1. Invest in EID alert networks for early detection using mobile technologies and RFID tagging;*	**This should increase the preparedness and responsiveness to EID outbreaks;**	**Early detection will become the norm and data for models will be able to help create agile, predictive models;**	**C-NS systems should be in place to enable a strong capability, being continually updated with real time data;**
2. Work to align border and key traffic point screening throughout the region;*	**Initially this will strengthen and align the region's defences against EID;**	**By using traffic points as key development venues for UC- NS development, APEC can become a global leader in EID management;**	**An effective, seamless system of key monitoring and modeling nodes can enable APEC to move toward eradication of EID threats;**
3. Support enhanced public health – UC-NS linkages to accelerate development of models for pathogen characterization, climate and land use factors and disease spread;	Asia-Pacific remains a region vulnerable to EID and so the intensification of broad and diverse expert networks represent a major new asset for the region;	APEC economies can become global leaders in modeling and management of EID threats – and many new technology applications that can be anticipated (see above Tables for examples);	APEC economies should be positioned as technology-wealth leaders from the applications of advanced UC-NS capabilities, as health care and longevity become key economic drivers by 2020;
4. Encourage the development of collaborative E Science platforms for research across the region into new UC-NS applications (focused on EID, but with broader applications envisaged;	E Science platforms are only in their first decade of development- by initiating strong R&D programs, APEC can show the way globally;	By 2015, R&D should be delivering commercial results that can lead to further enhancements of EID management and UC-NS innovations and widespread deployment;	By starting early on the research and deployment of UC-NS, the APEC region should be able to run ahead of other regions in realizing health opportunities from having highly developed EID management;



5. Develop EID training systems region-wide and link these into the projects that are developing UC-NS infrastructure and modeling for EID prevention, detection, mitigation and management;	The region has a young, technically trainable workforce that can provide the impetus for major development opportunities and definition of new types of jobs linked to UC-NS;	By 2015, today's 12 year olds will be ready for advanced education and/or the workforce – so having a top grade training capacity will be a major competitive asset for the region's future;	A strong and continuing commitment to training for UC-NS whether focused on EID or other applications by 2020 should be delivering benefits on many levels and to all the economies of the region.

* **Recommendations one and two should be the focus for immediate and mid term policy action. If these can be developed within the coming decade, the capacity for a UC-NS approach to EID will be strategically positioned for the future when more powerful and cheaper systems will be accessible throughout the region.**

In summary, the UC-NS technology road map (Table 11) and the resulting policy recommendations (Table 12) point toward many promising opportunities to apply new computation based capabilities to the prevention, detection, mitigation and management of EID, with potential spin offs into other socio-economic domains. By adopting these opportunities, APEC now can pursue an ambitious plan with which it could accelerate regional development and innovation before being besieged by another crisis such as SARS or Avian Influenza.

The network of experts involved in this process believes this to be a cause worthy of APECs priority attention and would be willing to reconvene to help further elaborate the possibilities and realize the potentials identified in this road map.

Finally, the network of experts involved in the EID Converging Technologies project also has some general ideas and key messages related to the UC-NS technology road mapping which it believes should be the basis for subsequent discussion and action on the part of APEC leaders during the period 2008-2020:

Key Messages

- ***Effective protection against EID threats requires interpersonal vigilance, collaboration trust and effective tools and institutional support systems. The project has first and foremost successfully developed a very skilled and collaborative human (consisting of both newly exchanged knowledge and trust in others knowledge) network of experts with broad reach across APEC. This in itself constitutes an important resource for EID management going forward.***

- ***Having state-of-the-art tools and information resources is increasingly essential for expert rapid deployment against EIDs. This project has demonstrated a range of new tools, from diagnostics and vaccines to modeling and UC-NS potentials that can be started soon. This ability to both imagine future needs and to consider how their application can be best integrated is clearly a key success factor of the project. It points to the value of continuing to build a robust technology and EID foresight capability throughout the region.***
- ***The focus on early alert, rapid sharing of knowledge so EID can be both characterized and screened for at traffic points, lays the basis for further collaborative work necessary to ensure continuous innovation and creation of a robust advanced system that can rely upon UC-NS when they actually reach a critical mass of distribution and experience. In this context the Canadian IDRC project that was presented at the Bangkok final EID session represents an excellent example.***
- ***The technical teams realized that it is not too early to define the specifications and performance characteristics that UC-NS will be based upon eventually and that this knowledge can immediately support leading edge preparedness in related domains such as against bio-terror threats, or for ecological systems monitors for climatic change.***
- ***There are already some indications of accelerated opportunities in technology applications such as: security screening; genomic data management and integration; mechanized electronic nose detection and molecular sensors which strengthen the case for further development of UC-NS for EID.***
- ***Pathogen detection, screening and characterization are already subject to expert systems; now the technology should be ready to proceed to the next step in a chain toward meeting the user requirements for UC-NS.***

In conclusion, the APEC project team and its network of experts wishes to express its appreciation to the hosts of the meetings in Phang Nga, Tokyo, Taipei and Bangkok for the opportunity to contribute to this important foresight to address EID in the Asia-Pacific region. If even only a few of the opportunities and innovations identified in this report can be developed by 2020, the health prospects for the region will have been immeasurably improved.

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Chapter Six: Diagnostics

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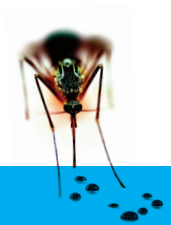
Introduction to Diagnostics

The response to disease

When a person is infected with a pathogen, the immune system responds by producing specific antibodies against that pathogen. Among various types of antibodies generated in response to infection, immunoglobulin IgM is produced first followed by IgG. It usually takes 1 week or more after infection for sufficient antibody to be produced to enable detection. For example in dengue fever, the dominant immunoglobulin isotype is IgM[1]. IgM levels rise quickly and appear to peak about 2 weeks after the onset of symptoms, they then decline to undetectable levels over 2-3 months. Anti-dengue IgG appears shortly after the peak of IgM. In a primary infection of persons never previously infected with a flavivirus nor immunized with flavivirus vaccine (e.g. yellow fever, Japanese encephalitis, tick-borne encephalitis), IgM level is high enough to detect. In contrast, a secondary infection results in the appearance of higher levels of anti-dengue IgG. Therefore, both tests should be available in dengue endemic areas. Dengue-specific antigen detection systems have also newly been available commercially.

Current diagnostic technologies

Diagnosis of infectious diseases is done by detecting causative agents (virus, bacterium, etc) and/or anti-pathogen antibodies. The former includes antigen detection, genetic and cultivation methods (Figure 6).



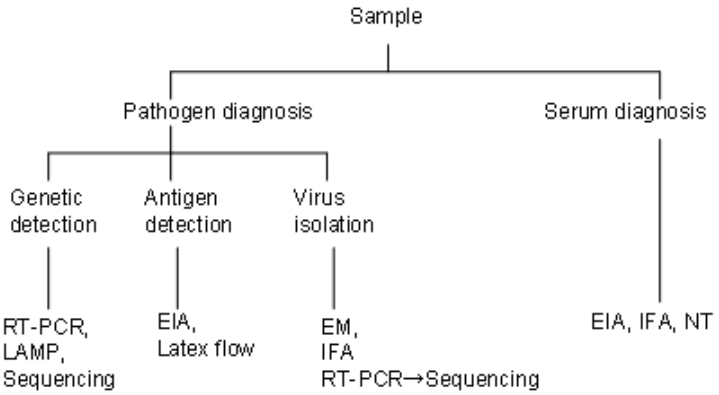


Figure 6: Diagnosis methods for infectious diseases: enzyme immunoassay (EIA); indirect fluorescence antigen (IFA); neutralization testing (NT)

For determinative identification of pathogens, visualization under the microscope, with or without staining, electron microscopy and cultivation of the organism are conventional tools. Cultivation and isolation is still frequently for bacteria and viruses. However, it is generally time-consuming or even impossible to do for some pathogens and is not a front line diagnostic tool.
Immunodetection methods that measure increased antibody levels or detect antigens are widely used. Antigens are proteins, lipids, polysaccharides, or nucleotides derived from pathogens, which induce the host's immune system to generate antibodies. An appropriate second antibody can be developed as a tool for detecting antigens. Early in infection, antibody levels are low and infection may not be detected. At this time pathogen detection is required. However in many infections it is possible to detect pathogens for a short period only (several days in the case of viral infections).

Enzyme-linked immunosorbent assay

Common immunological tests are based on the enzyme-linked immunosorbent assay (ELISA) and the immunochromatographic technologies[2]. These tests can detect both antigen and antibody. ELISA is an assay with several steps: coating of antigens onto the surface of plastic wells, the addition of serum samples to the wells and several washing stages. Antigen–antibody reactions are visualized using anti-human (or other species as appropriate) antibody linked to an enzymatic indicator system (color, fluorescence, etc.). The assay takes several hours to perform even using commercially available diagnostic kits. ELISA tests are relatively easy to perform and can be fully automated. ELISA tests of various types are likely to remain an important tool in diagnostic laboratories in the future.

Immunochromatographic tests and other point-of-care systems

These are mostly based on lateral flow systems and can be used to detect pathogens, antibody or antigens. Lateral flow immunoassays are simple one-step or two-step assays for the qualitative determination of antibody directly from blood or serum or for the detection of a pathogen from a sample or specimen. Beside its fast performance, the detection of analytes (molecules like antibodies and antigens from pathogens) directly from whole blood, urine or other body fluids without any further treatment is one of the major advantages of these rapid tests.

A rapid lateral flow test consists of a system of overlapping membranes containing the dried components needed for the test performance. These membranes are assembled to small strips which are often placed into a plastic housing for better handling (Figure 1).

The sample is loaded to a sample application pad. In the case of whole blood/capillary blood samples, a separation of blood cells and plasma takes place. The liquid fraction of the patients sample diffuses through the so-called conjugate release pad containing labeled detection molecules. The conjugate molecules are specifically directed against the analyte of interest. The conjugate is re-dissolved and the analyte is specifically bound by the conjugate.

The analyte-conjugate complex further diffuses through the analytical membrane. On this membrane mostly two lines are arranged one after the other: (i) the test line containing analyte-specific molecules responsible for immobilizing the analyte- conjugate complexes and (ii) the control line fixing non-bound conjugate particles indicating that the conjugate is active. The color intensity of the test line is related to the analyte concentration in the test sample. If the analyte of interest is available above the detection limit the test line and the control line are clearly visible. On the other hand, if the analyte is below the detection limit only the control line appears during test time. The last component of the rapid test is the wicking pad which simply collects the fluid running through the test system and preventing backflow of the fluid through the test system. There are a number of variations on this basic system in use.

Lateral flow tests have similar levels of sensitivity to the traditional ELISA technology. The technology is very cheap, long-lasting and can be used in any system for which reagents are available. The challenge with these technologies is to ensure that they are appropriately deployed, validated and maintained. The use of lateral flow diagnostics in the public health sector raises questions about self diagnosis and medication. In many circumstances this is not desirable and can lead to enhanced drug resistance.

An example of the need for this type of technology is in the detection of bird flu. Current point-of-care tests do not generally have adequate sensitivity to detect virus early enough to allow most effective treatment with anti-influenza drugs. The later treatment of influenza with drugs and/or self medication will enhance the development of resistance which is already becoming a problem.

A collaboration research group from the International Medical Center of Japan has

played a major role to develop a rapid diagnostic kit for highly pathogenic avian influenza H5N1 infection in human. This kit could be useful for a diagnosis within 15 min at patient bedside and quarantine as appeared in domestic newspapers of May 9.[3]

There are a number of alternative rapid point-of-care tests on the market. However, few if any offer additional advantages over the lateral flow technology and can be more expensive. For developing countries with limited laboratory resources and access (Type A, details on ROLES OF DIAGNOSTICS IN COMBATING EID session), an immunochromatographic test would be a preferred method.

One of the major limitations of lateral flow technologies is a lack of sensitivity for pathogen detection. This problem may be addressed by the development of portable nucleic acid amplification systems such as real time PCR based on micro-fluidic technologies or LAMP technology (see below). Such technologies will have higher sensitivity and be rapidly deployable. While the portable PCR technology has been under development for some years the lack of deployment suggests that further development is required. In the short term, tests of this type are likely to be quite expensive. Hence, further development may be required to achieve sufficient cost benefit.

Molecular tests based on polymerase chain reaction (PCR)

Antibody detection tests are the most widely utilized diagnostic technique especially in developed countries. In some situations it can be difficult to discriminate between antibody resulting from natural infection and that resulting from vaccination. Another issue is co-infection with HIV. It is reported that there are some cases of HIV and hepatitis C co-infection where patients do not develop hepatitis C antibodies[4].
The invention of a molecular technology to amplify a specific region of DNA has dramatically expanded pathogen detection possibilities. The technology, named polymerase chain reaction (PCR) allows the DNA to be amplified a billion fold. It is not only used for diagnosis, but also for other biological testing, e.g. for the detection of genetically modified foods.
The conventional PCR method requires the use of gel electrophoresis for detection of products followed by sequencing of the products for definitive diagnosis. This is relatively slow. The more recent introduction of real-time platforms for PCR (RT-PCR) has revolutionized molecular diagnostic detection methods in clinical microbiology[5]. This technology has been in widespread use in research laboratories since the early to mid nineties. As the name suggests, real time PCR is a technique used to monitor the progress of a PCR reaction in real time. At the same time, a relatively small amount of PCR product (DNA, cDNA or RNA) can be quantified. RT-PCR is based on the detection of the fluorescence produced by a reporter molecule which increases as the reaction proceeds. This occurs due to the accumulation of the PCR product with each cycle of amplification. These fluorescent reporter molecules include dyes that bind to the double-stranded DNA (i.e. SYBR® Green) or sequence specific probes (i.e. Molecular

Beacons or TaqMan® Probes). RT-PCR facilitates the monitoring of the reaction as it progresses. One can start with very small amounts of nucleic acid and quantify the end product accurately. These closed-tube systems virtually eliminate the risk of amplicon carryover because the samples are not opened following thermal cycling. Moreover, there is no need for the post PCR processing or sequencing which saves the resources and time. These advantages of the fluorescence based RT-PCR technique have completely revolutionized the approach to PCR-based quantification of DNA and RNA. RT-PCR assays are now easy to perform, have high sensitivity, more specificity and provide scope for automation. Real time reverse transcriptase PCR requires an additional cycle of reverse transcription that leads to formation of a DNA molecule from a RNA molecule. This enables the detection of RNA.

The application of the technology in disease diagnosis has been widespread. From a technical perspective, the technology is now relatively simple and tests can be performed easily in any laboratory with a molecular biology capability and the appropriate infrastructure. Many RT-PCR tests are in use for the detection of nucleic acid from a wide array of pathogens. However, there has been little attempt to standardize and validate these tests. There are a number of RT-PCR platforms on the market that use different systems. This adds some complexities to standardization and validation. The design of primers remains critical and requires informatics expertise if the test is to be of maximum benefit. Contamination can also introduce difficulties. If the appropriate quality control is not in place, false positive results can be common. This can be a significant problem in critical index case diagnosis.

A positive RT-PCR result does not automatically mean that a live organism is present as the test will detect nucleic acid in dead organisms. These factors introduce considerable variability into testing and hence interpretation of results. The application of this technology in the diagnosis of a primary index case of infection differs from its application in a control program. Hence index case diagnosis may be better undertaken in a quality controlled laboratory environment using a validated test in combination with other tests. Testing as a part of a control program could be undertaken in a less stringent environment. However the implications of particular results need to be considered in the context of the outbreak.

It is possible to undertake multiple reactions on the same sample at the same time, a process known as multiplex PCR. Multiplex PCR, first developed in 1988 by Chamberlain et al., is now widely used for detecting variation of species or mutants.[6,7].

Novel technologies

Those technologies that have been described above are generally used for the detection of known pathogens. The detection of unknown pathogens requires a different approach. The technologies for capturing new pathogens are well reviewed in the paper written by Lipkin.[8]

He summarized new technologies useful to identify unknown pathogens as follows;

"It is necessary to do some multiplex assays which detect many candidates at once. The number of candidates considered can range from less than ten with multiplex PCR, to thousands with microarrays, to the entire tree of life with High-throughput Sequencing (HTS). Costs and ease of use are improving; nonetheless, only multiplex PCR assays are widely used at present. In microarrays and HTS, many genetic targets compete for assay components (e.g., nucleotides, polymerases and dyes), in some instances with different efficiencies. This abrogates quantitation and reduces sensitivity."

In parallel with the rapid advances in diagnostic technologies, there have been significant discoveries in areas such as nanotechnology, micro-fluidics, information technology and fabrication. Coupling the advances in these technologies with the major advances in serological and molecular diagnosis has meant that completely new approaches to the diagnosis and detection of infectious diseases are possible.

Microarrays

This technology enables testing for the presence of nucleic acid from many (thousands) pathogens at one time. DNA microarrays are small, solid supports onto which the sequences from thousands of different genes are immobilized, or attached, at fixed locations. The supports themselves are usually glass microscope slides, but can also be silicon chips or nylon membranes. The DNA is printed, spotted, or actually synthesized directly onto the support. Microarrays are a significant advance, both because they may contain a very large number of nucleotides and because of their small size. Microarrays are therefore useful when one wants to survey for a large number of genes quickly or when the sample to be studied is small. They may be used to assay gene expression within a single sample or to compare gene expression in two different cell types or tissue samples, such as in healthy and diseased tissue. Because a microarray can be used to examine the expression of hundreds or thousands of genes at once, it promises to revolutionize the way scientists examine gene expression. This can result in the generation of vast amounts of information.

This technology has immediate application in the identification of new pathogens that cause emerging infectious disease. Indeed, it was through the use of this technology that the virus causing SARS was first identified.[9] It should be recognized that this is a screening technology that may assist in the identification of an unknown virus. Sensitivity of such technology is low and inevitably some preliminary amplification is required.

Pan-pathogen arrays have been developed that contain nucleic acid probes for virtually all known pathogens. However it is virtually impossible to validate very large arrays so index case diagnosis must always be accompanied by additional diagnosis. The interpretation of all of the data may require considerable informatics expertise. Where

large arrays are involved, the amount of data generated is large and good analytical capacity is needed.

Bead arrays

A new technology which is emerging involves the used of micro-spheres to which analytes can be coupled. Unlike PCR and 2 dimensional array technologies, this can be applied to both detection of nucleic acid (pathogen detection) and antibody (evidence of host infection). The technology only requires very small samples and can be automated. The liquid bead array uses color-coded microspheres to carry discrete assays within a single volume, but does not require that the particles be captured or immobilized in order to distinguish individual results. Detection is carried out using flow cytometry, which allows the suspension of differently colored beads to remain in suspension throughout the entire assay and its detection. The level of multiplexing on such arrays is limited by the ability to simultaneously discriminate different spectral signatures. The leading platform for liquid bead arrays is xMAP technology (Luminex), with the Cytometric Bead Array (BD, or Becton Dickinson) also producing many applications. Future developments will permit the use of very large bead sets.

High throughput sequencing

A further genetic technology which is becoming more widespread is high throughput sequencing. A number of companies have developed technologies that produce millions of raw bases per hour on a single instrument. Pathogen genomes can now be rapidly sequenced without the time or cost constraints of current DNA sequencing methods. Specific software enabling mapping or *de novo* assembly for whole genomes has also been developed. For example, it is now possible to sequence a typical bacterial genome in days without cloning and colony picking.

This technology will become a front line diagnostic tool in the near future. This technology can be applied only with a sophisticated bioinformatics technology to eliminate huge amount of host's genome. The problem has overcome by the team of Osaka University and RIKEN (RAPID, see below) The identification of an unknown pathogen in a tissue sample from an infected patient has been achieved using this technology. One of the other major benefits is that the technology enables rapid genotyping to identify pathogen variants. This is becoming increasingly important as more cases of pathogenic variants causing disease epidemics emerge. The cost will continue to decrease with a full viral genome now able to be sequenced for less than USD$50,000. For this type of technology to be useful, a substantial informatics capacity is required. In the short term this type of technology will be coupled with other molecular diagnostic tools that increase the likelihood of success and reduce the cost.

New Technologies that are under development in Japan under the "Program of Founding Research Centers for Emerging and Re-emerging Infectious Diseases"

Japanese government's project namely "Program of Founding Research Centers for Emerging and Re-emerging Infectious Diseases" (FRC Program) (details will be mentioned later, in Chapter 4) has emphasized on developing new diagnostic technologies. RIKEN is the institute that conducts comprehensive research in science and technology. Some researchers belonging to FRC Program got together to develop new diagnostic technologies by collaborating with RIKEN.
Nagai and Okamoto from Center of Research Network for Infectious Diseases (CRNID) gave a presentation about these diagnostic technologies at TRM workshop held in Tokyo. They are summarized here as follows (Table 1).

Table 13: Comparison of three gene amplification technologies

	PCR	LAMP	SMAP
Developed by	Roche Diagnostics, Co. Ltd.	Eiken Chem. Co. Ltd.	RIKRN and Dnaform Co. Ltd.
Amplification temperature	Thermal Cycling (4C – 95C)	Isothermal (65 C)	Isothermal (60C)
Sensitivity	High	High	High
Cost for equipments	High	Very Low	Low
Feature	Conventional	Low cost fast detection	Fastest detection High fidelity (useful for SNPs analysis)
Disadvantage	Time (1.5 hr)	Difficult primer design	Difficult primer design

LAMP

Loop-mediated Isothermal Amplification (LAMP) is a simple, rapid, specific and cost-effective nucleic acid amplification method developed by Eiken Chemical Co., Ltd. This technology has a big advantage that the whole amplification reaction takes place continuously under isothermal conditions temperature (approximately 65°C). It has been attracted by many researchers in the FRC Program as a cheap, sensitive and specific diagnostic technology[10-13] (Figure. 7).

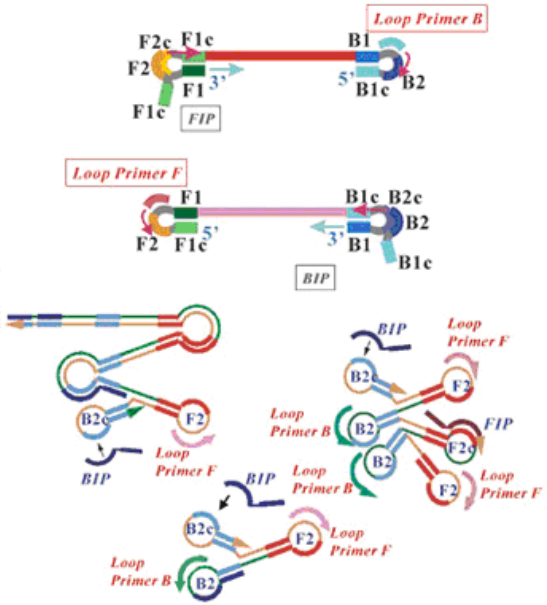


Figure 7A: Principle of LAMP technology.

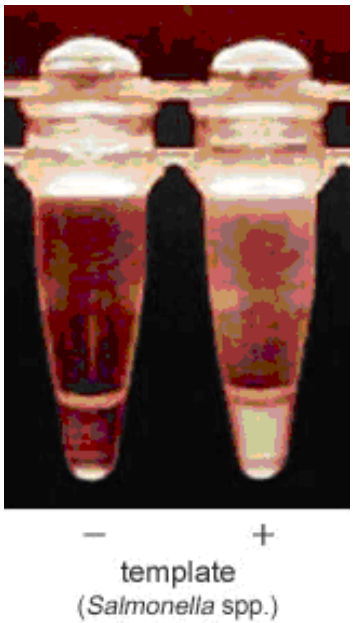


Figure 7B: LAMP result can be visuallyobserved by turbidity.

SMAP

SMart Amplification Process (SMAP) method is the newest technology developed by RIKEN group. This technology is for gene amplification with constant temperature, similar to LAMP. As SMAP is too accurate to amplify a gene with a point mutation, it can be applied for SNPs analyzes[14,15] (Figure. 7).

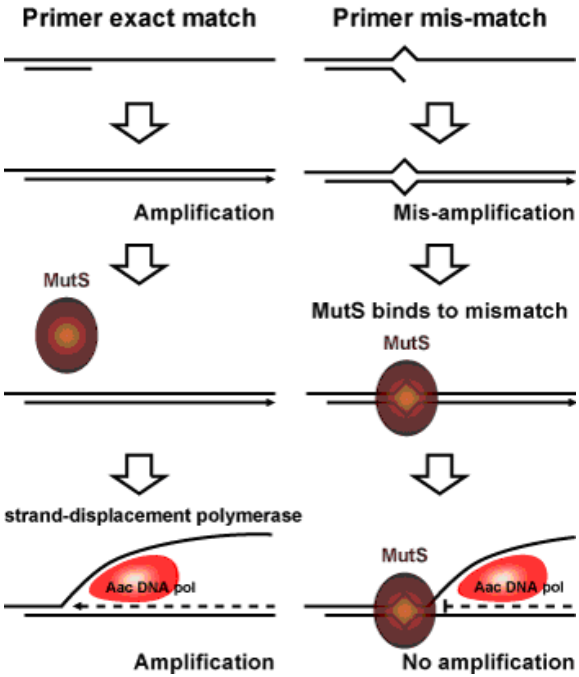


Figure 8: Principle of SMAP technology for SNPs analyzes.

Avian influenza H5N1 has been continuously causing outbreaks in poultries. It is highly concerned that some mutations in the virus may cause human pandemic. The collaborative project between the Tokyo University and RIKEN started to use SMAP to monitor the mutations responsible for Tamiflu resistance, increased affinity to the human receptor and human pathogenicity.

RAPID

The most commonly used method of sequencing DNA - the dideoxy or chain termination method - was developed by Fred Sanger in 1977 (for which he won his second Nobel Prize). Sanger also introduced a technique, named shotgun sequencing, in 1982, in which sequencing begins by physically breaking the DNA into millions of random fragments[16].

Those technologies then lead to the invention of high-throughput sequencing technology, combining with other innovations (e.g. pyrosequencing) and the development of IT[17]. 454 Life Sciences, a Roche Company, develops and commercializes the innovative Genome Sequencer™ system for ultra-high-throughput DNA sequencing. The genome sequencer FLX generates 100 million high quality bases per 7.5-hour instrument run. The detail of the sequence technology is summarized in the company's web site[18].
By employing this technology, Osaka University and RIKEN have been developing a new method to identify pathogen of EID rapidly, named Robotics assisted-Pathogen Identification (RAPID) (Figure 9).

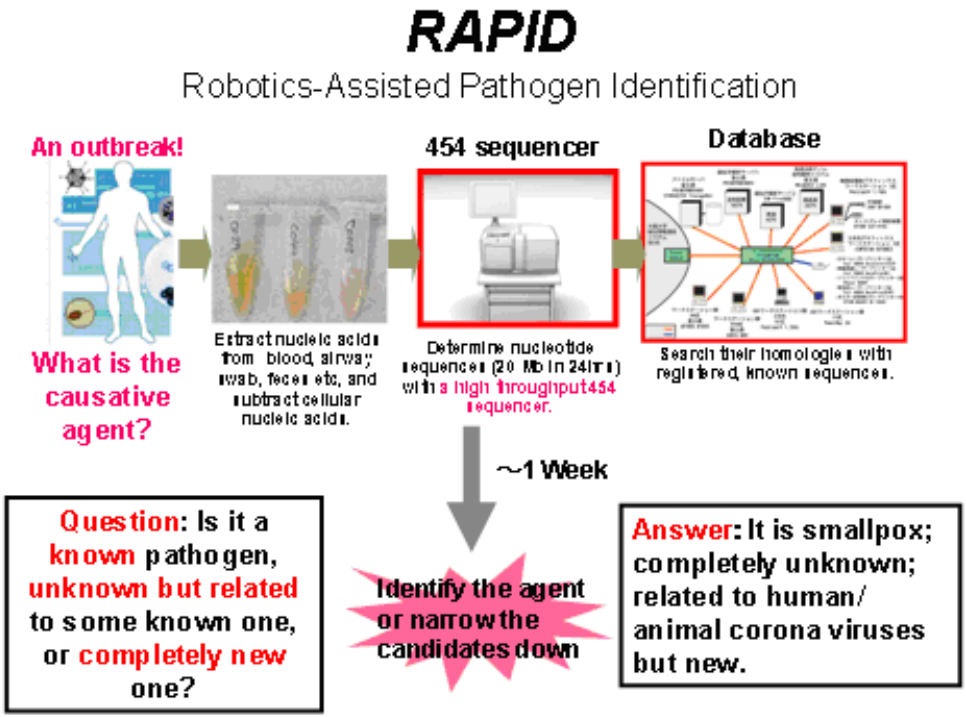


Figure 9: RAPID is for identification of unknown pathogens.

DNA or RNA extracted from clinical samples, such as blood, sputum, stool etc., is applied on the sequencing. Sequencing result can be obtained within 24 hours, as 200 thousands of the "100base". As more than 99.9% of the data are human origin, the success of this technology owes a lot to a data processing technology (IT). Osaka University has succeeded in developing a high-performance data analysis system with some technological improvements such as an in-house database, an algorithm for subtracting human genomic information and so on.

The project team reported a successful direct detection of the causative bacterium in a diarrheal human sample by this technology[19]. The group of Columbia University also published the identification of new virus using High-throughput sequencing method.[20,21]

The challenges

These new approaches raise a plethora of social and political issues. As tests become faster, cheaper and more reliable, it is reasonable to ask who should have access to the tests, who will perform the tests and how will the results be used. In the area of emerging infectious disease, an incorrect diagnosis could have significant adverse consequences. In contrast, as the notion of personalized medicine develops, the demand for point-of-care and personalized diagnostic tests will increase. It is against this background of advances in technologies and increased concern for personal health and well-being, we will need to make decisions and set priorities regarding disease control and management.

Due to the social, economic and political complexities it is unlikely that personal diagnostics for emerging infectious disease will be deployed in a widespread manner in the near future. Such testing may be applicable in the management of a large outbreak but it is difficult to see how such tests could be manufactured and deployed in the face of an outbreak. This is in contrast to the use of tests for the measurement of more general physiological parameters such as blood sugar, blood pressure, cholesterol and pregnancy detection.

Bioinformatics in the broadest sense is a significant issue with tests already generating large amounts of data. The data collection, data analysis and interpretation of this data remains a challenge.

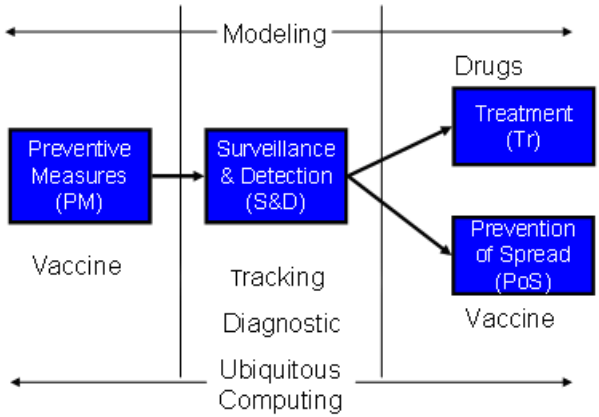
Many technologies that are developed and used in a research environment require considerable additional development before they are suitable for application in a routine diagnosis. Similarly, some diagnostic technologies that are suitable for application in disease control programs and in response to disease outbreaks are not suitable for wider use in surveillance programs or for broader use in the community. It is essential that tests are used in a manner that is consistent with the purpose for which they were designed.

As new technologies are developed and deployed, the scientific, social and political implications need to be considered on a case by case basis. In order to obtain valid information on which to base critical disease management decisions, tests must be used for the intended purpose and performed in a quality controlled environment in an accredited laboratory. Tests developed and used in the broader scientific community as well as used in the community at large will inevitably be used in a variety of circumstances. This does not mean that the information is not useful of valid but must be considered

within the context in which it is obtained. It is difficult for disease managers, regulators and politicians to understand and address this issue.

Roles of Diagnostics in Combating EID

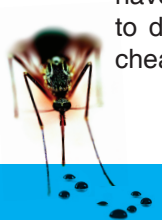
Diagnosis plays a critical role in the treatment of disease and in developing response strategies. In an outbreak situation, vaccination may need to be accompanied by a diagnostic test that can discriminate between the response to a vaccine and a natural infection. Appropriate diagnostic technologies are also critical for surveillance programs. Diagnostic technology also plays a crucial role in the prevention of spread. Hence diagnostic technologies are relevant to all stages of the EID model below (refered to figure 5 on page 35).



It is important to note that the tests used in index case diagnosis, pathogen characterization, in a control program and in the eventual eradication, may all differ. The use of a test that is fit for purpose is very important.

Type A tests are used at the primary healthcare level, where the majority of patients present with symptoms. These include local healthcare centers and clinics that may be in remote areas or refugee camps. They are not well equipped; sometimes not even having access to refrigeration. They are often poorly resourced and suffer from a lack of staff. The diagnostic technologies must be cheap, easy to use and not require sophisticated technology. Some nonprofit organizations will sometimes buy this type of diagnostic system and distribute them to developing countries. In developed countries, there is a role for this type of test in the general practitioners clinic, particularly for endemic and chronic diseases.

Type B tests are used in the district and national health centers. These centers will have the responsibility to make the primary or index case diagnosis. They usually have to deal with hundreds of samples daily, therefore, high-throughput, high quality and cheap technology is required.



Type C tests are used in sophisticated high-technology diagnostic centers. The role of such centers includes the investigation of unknown infectious diseases in response to a disease outbreak of unknown etiology. The results of diagnostic testing in such centers may be provided to governments and disease management authorities who have the responsibility for releasing information to domestic government and international agencies. Such centers would also be expected to study the biology of causative agents. Thus, they require access to the latest technologies and containment facilities.

In order to use information from a diagnosis effectively, systems for the collection and sharing information needs to be available. Such information can arise from the use of any test.

Roadmap Discussion

The discussion held in Tokyo is summarized in Table 14 and is outlined below.

Table 14: Technology roadmap for diagnostics

A roadmap for the development of diagnostic technologies to combat emerging infectious disease				
		2007 - 2011	2012 - 2017	Beyond 2017
User's requirement		Validated, easy to use in the field or local site, low cost, suitable for developed and developing countries, no cold chain required. Higher sensitivity and specificity	Low cost testing for many infectious agents simultaneously Ability to test large numbers of people in a non-interventionist manner Broad screening tools Improved border biosecurity	Personalised medicine with testing linked to information networks and personalised treatment
		High throughput technologies	Rapid genetic characterization of pathogen, high biosecurity level capacity	
		Access to the latest technologies	Automated data collection and analysis	
Technology		**Towards low cost, high sensitivity and specificity, rapid, multi-agent diagnostic devices linked to automated data collection and analysis** **Highly competent drugs**		

	Local site	Lateral flow and other point-of-care devices, low cost	Low cost tests of greater sensitivity- gene amplification Screening technologies for airports, thermal, chemical	Chemical sensing
	Regional Health Centers	Rapid high throughput systems, high PCR capacity.	High throughput genetic sequencing. Multiplex testing	
	International Institutions	Access to latest and developing diagnostic technologies	A high level investigative capacity and capability	
		Validation processes established	Information collection and sharing system from the local diagnostic systems through to the International Institutions	Personal Diagnostic Devices, implantable or wearable biosensor -transmitter
Challenges	Technical	Sensing systems of adequate sensitivity,		
		Low cost, point-of-care amplification systems		
		Effective networks to collect, manage and analyze data		
	Social, Economical, Political	National laboratory hierarchy accepted Acceptance of information collection processes Privacy concerns addressed The use of point-of-care and personal diagnostic technologies in the community without adverse implications Education and communication to the public (to get the public understanding for the significance of EID control).		
		Ownership and sharing of biological material		
APEC-Collaboration		Long-termed budget system for EID technology development and deployment, APEC “Centers of Excellence”		
Projects		Validation standards developed Laboratory hierarchy strategy developed	National (and international) information sharing systems developed	BSL3-4 capability developed

Type A tests

Current diagnostic technologies are based on either immunological and genetic detection. The immunochromatographic method is recommended by the WHO for most of viral infections, because of its low cost and the simplicity of the reaction. For example, in a primary healthcare setting, type A influenza virus can be identified by immunochromatography all over the world. The cost is as low which meets WHO needs. Sensitivity is adequate but not high enough for triggering anti-viral therapy. Such assays may not detect antigenic variants as the mutation rate in influenza virus is high. For some viral infections, it is recommended that testing be performed twice in order to compare the antibody level but this requires the patients to visit the hospital twice. On the other hand, diagnosis based on genetic detection is more sensitive. To do this, a specific region of viral/bacterial genes needs to be amplified. PCR has been the only and the best way to achieve such amplification. This technology needs a specialized equipment and enzymes requiring refrigeration.

User's requirements in this category listed in the roadmap discussion held in Tokyo were technology without equipment (refrigerator, centrifuge etc.) and development of long-lasting agents.

(1) Immunological detection of antigen:

The systems expected within 5 years As stated above, additional immunochromatographic systems to detect a wider range of pathogen antigens should be developed. Such developments require interactions with commercial diagnostic test manufacturers as there will not be a commercial market for many tests.

The systems expected within 10 years The development of flexible systems that enable the rapid response to changes in pathogens is required. Such systems may involve genetically engineered recombinant antibodies that can be selected to bind to variant viruses and other pathogens.

The use of portable diagnostic devices will increasingly be linked to automatic reporting systems. With increasing speed of mobile phone networks and the direct connection to web databases, it is not difficult to see diagnostic tests performed with the automatic transmission of the result to a data system that allows disease managers to analyze and report data in near real time.

Implantable sensing technologies that detect sero-conversion will be common in animals. All high value livestock will have implantable systems for identification and tracking, monitoring of physiological parameters and key diseases. The measurement of critical physiological parameters may well provide an indicator of any infectious disease.

(2) Genetic detection

PCR is the most widely utilized technology for this type of diagnosis. It is mainly used in well-equipped laboratories in the categories B and C since the technology requires a specialized equipment. For Type A testing, machineless gene amplification technologies are required. LAMP technology is one of the strongest candidates. It amplifies specific genes with constant temperature, usually around 65°C. In addition, the result can be visually detected by turbidity. EIKEN Co. Ltd. has also developed a new kit providing a sample purification membrane and reaction reagents in one tube[22]. This addresses the need for long-lasting reagents. However, testing of this type still needs an apparatus to keep the temperature for reaction at around 65°C. For use in the clinics in refugee camps, the whole reaction should be completed at a room temperature.

The systems expected within 5 years Improved LAMP or similar amplification technology, which is performed at room temperature, using enzymes and reagents that are stable at ambient temperatures. A cheap micro-fluidic based real time PCR test for influenza could be used in a pharmacy or doctor's room with an on the spot decision made concerning treatment. Such a test could be similarly deployed in animal disease diagnosis. Tests such as this could be available for a range of pathogens.

Type B tests

The high-throughput as well as high-quality technology is required in this category. Even with an advanced technology, the total procedure should be such that it is simple to achieve a high level of reproducibility and quality control. PCR is one of the most popular technologies that meet the above requirements. WHO guidelines include recommendations on this technology for many kinds of infectious diseases, including avian influenza.

Each center or laboratory in this category has different requirements and may require different technologies. Different categories are:

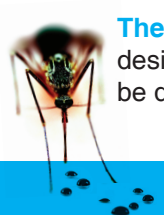
1. Regional/National healthcare centers and hospitals

2. Airport, seaport, or border checkpoint

Regional and national healthcare centers

Regional and national healthcare centers have to handle hundreds of clinical samples each day, so simple and high-throughput methods are required. Currently more than a hundred samples can be applied to a RT-PCR reaction. However, it needs at least 1-2 hours to obtain a result. New technology is expected to simplify the steps.

The systems expected within 5 years A faster, simpler and cheaper technology is desirable in this category. Combination of antibody and genetic detecting system would be desirable, so that all samples with any stage of illness can be diagnosed.



The role of the regional/national diagnostic center is to determine the causative agents officially. The results should directly affect governmental decisions. In addition, the international society usually expects to share the information obtained. Advanced technology is needed in such a center, as well as an international information network. Regarding this issue, democratic and economical improvement is more important than that of technology.

In the small size of health centers, clinics or hospitals of developed countries are where the patients first visit with infections. The developed countries have the problems that either doctors or healthcare workers are not familiar with infectious diseases, especially tropical diseases. Since technology is advanced enough, as an assumption, it is necessary to build a good information system. It includes the system to bring the patient's sample of unknown infections as quickly as possible to the diagnostic centers, sufficient training of the healthcare staff and/or enough number of hospitals to accommodate the patients. New technology is also expected as follows.

The systems expected within 10 years The technology useful to distinguish infectious diseases from other non-infectious ones is needed. It currently relies on the observation of the clinical symptoms[23]. If there are some good biochemical markers to determine the infection (especially viral ones), they would be highly helpful to make a plan for treatment.

The role of airports with regards to EID

Quarantine:

The systems expected within 5 years If a pandemic occurs, the passengers suspected of being infected will be confined (in the airport) until they are confirmed as free of infection. Therefore, there may be a need to improve or build diagnostic preparedness in an airport. LAMP may be best technology to meet such a need.

The systems expected within 10 years Following the SARS outbreak, some airports introduced a system for monitoring body temperature of all passengers. Such a system could be extended to monitor each passenger's physical condition as a whole. Sensing systems that detect a chemical footprint of a pathogen could also be developed.

Controlling of imported animals/insects

Many tropical diseases are vectored by animals and insects. The USA has experienced a West Nile virus pandemic since 1999 which is spread by mosquitoes. Exotic mosquitoes imported with used tires have most likely contributed to the spread. Once an exotic mosquito enters an economy, it will be very difficult to control them. It is necessary to develop tools to reduce the likelihood of entry. So far, this remains a challenge.

Type C tests

1. National diagnostic centers or Regional reference laboratories of WHO

2. University laboratories

Both National diagnostic centers and university laboratories are common in having sophisticated technology and leading-edge knowledge. However they do serve different purposes. National diagnostic centers and WHO Regional reference laboratories are in charge of taking countermeasures after the identification of the causative agent. The latter includes various researchers studying infectious diseases and has lesser disease response responsibility. However, many researchers in universities are also involved in National diagnostic centers, often providing guidance and expertise. The most expected improvement is not so much in technology but in a global system that can rapidly identify infectious agents and share information. In addition, researchers in universities are expected to develop the new cutting edge technology and develop these technologies through collaboration with industries.

Policy Recommendations for Diagnostics

What is exactly needed for the new diagnosis?

Many infectious diseases can be adequately identified with the current technology. However, this often requires a relatively sophisticated laboratory. The tests may not be appropriate for point-of-care use or have not been made available. For the control of particular diseases the development and distribution of a cheap, sensitive and simple technology such as immunochromatography and LAMP would be of great benefit.

A good network for sharing knowledge, information and samples is very important to fight against transboundary infectious diseases.

We would like to propose the establishment an EID diagnostic network and building a virtual EID research and diagnosis center of infectious diseases in Asia.

Using this network, samples, information and human resources are shared in Asian countries. The center should include laboratories with cutting-edge technologies to perform research and diagnosis of unknown infections, include high-level containment facilities such as BSL-3 and -4 laboratories and include bioinformatics capability. The laboratories will also provide high level training for all clinicians and diagnosticians from national and regional diagnostic laboratories. This will ensure that the latest knowledge is fully shared in all national diagnostic centers in Asia.

The concept involves the use of existing institutions and networks and to expand spokes from hubs, which covers all Asian countries.

The Program of Founding Research Centers for Emerging and Re-emerging Infectious Diseases was implemented as a project commissioned by the Ministry of Education, Culture, Sports, Science and Technology (MEXT), Japan in 2005. Several universities and institutes were selected to build collaboration laboratories in Asian and African countries to study emerging and Re-emerging infectious diseases (ERID)[24]

The purpose of each collaboration laboratory is to establish good partnership with Asian or African research organization and researchers to study or analyze local samples collaboratively. The program also aims to nurture young researchers in both Japan and the counterpart countries expecting to contribute to this field in the future.

The Program established collaboration laboratories in Thailand, Viet Nam, China, Indonesia, India, Philippines, Zambia and Ghana. In addition to research projects such as surveillance, control, vaccine or drug development, we have been focusing on developing new technologies for diagnosis, exemplified as RAPID, SMAP and LAMP.

Here we have already had several EID research bases in Asian countries. It is recommended that a new network of sophisiticated EID research sites effectively for the benefit of the Asia be established. This network will have connections into other key human and animal disease diagnostic centers or networks such as CDC in USA , the Australian Animal health Laboratory in Geelong, Wellcome Trust network for tropical diseases and Institut Pasteur international network..

High-throughput sequencers and other cutting edge technologies will be available in these centers and every economy in the network uses the centers to determine undiagnosed infectious diseases. The sharing of samples, people and information is essential. The discussion at Tokyo suggested the possibility of APEC framework for this purpose. This Asian network should be collaborative with the WHO. But the Asian network will be able to react more quickly in the case of EID outbreak in the region.

Diagnostic capacity, capability and tools for emerging infectious diseases and some of existing diseases are still inadequate. Research into the application of technologies in disease diagnosis together with the study of disease biology should remain a priority.

In order to combat emerging infectious diseases, the new technologies need to be considered together with the social challenges. New technology alone will not suffice. Thus, the development of diagnostic tests for emerging infectious disease should also be considered in the context of the broader testing for endemic diseases in the human and animal health sectors. The recommendations have also been developed from a pragmatic perspective; trying to consider what is realistic to achieve amongst APEC member countries.

Recommendations

Short term

1. Diagnostic companies be encouraged to develop, maintain and validate rapid, cheap point-of-care tests for endemic and chronic diseases

Such rapid point-of-care tests are developed and validated for a specific purpose. It is important that they are used only for the purposes for which they have been developed. The inappropriate use of tests can result in incorrect diagnostic outcomes, which in some situations can have significant adverse consequences. Regulators and disease managers ensure that these tests are used only in the appropriate social and clinical environment.

In some situations it would be considered undesirable to have testing done outside a recognized diagnostic facility. Some test outcomes can have significant economic and political consequences.

2. Jurisdictions establish a network of well equipped, diagnostic laboratories.

Diagnostic laboratories of this type would provide routine diagnostic services (type B tests). These laboratories would have up-to-date, automated, validated diagnostic systems that will enable them to handle large sample numbers in a quality controlled environment.

3. Laboratories should be actively involved in quality assurance and test validation processes.

Each jurisdiction should develop a test quality assurance program. All laboratories in the networks at this level should be involved in such a program. Such a program requires a specific allocation of resources.

Medium term

1. Each jurisdiction has at least one laboratory that is equipped with the latest and most sophisticated diagnostic infrastructure. These laboratories should be interconnected to form Asian EID Diagnosis Center.

These laboratories should be connected and operate as a virtual center called “The Asian EID Diagnosis Center” This infrastructure will include array technologies, high throughput sequencing, gene amplification and micro-fluidics with biosecurity level three or four capability. In order to handle organisms causing emerging infectious disease, a laboratory must have a higher order biosecurity capability. In order to capture the benefits of the new molecular diagnostic technologies, significant bioinformatics

capability is required. The co-location of trans-disciplinary teams of research workers in the center will deliver the optimal benefits in regard to the development of new diagnostic platforms.

2. Asian EID Diagnosis Center should be resourced in such a manner that they are able to rapidly respond to disease outbreaks and developments in technology.

At this level, laboratories will be required to rapidly respond in the case of disease outbreaks. This will require a location of resources. These laboratories undertake both research and diagnostic activities related to emerging infectious disease. They will be staffed by the most creative and innovative disease researchers. A mixture of research and diagnostic development is required in order to attract and retain high-quality research workers. The combination of research and diagnostic activity also provides a "surge" capacity in response to an outbreak.

3. The Asian EID Diagnosis Center develops a close relationship with universities to provide a training environment to ensure that appropriately skilled scientists are available.

4. **Systems for the capture, management and analysis of data from testing should be developed at both laboratory and national levels. Such systems are linked to surveillance systems.**

This data can be used to determine trends and detect outbreaks. Near real time, web based data collection and analysis systems need be developed.

5. International connections between information management systems should be developed with the appropriate levels of security and confidentiality developed and maintained.

International networks are essential to combat the trans-boundary nature of EID spread.

6. Closer connections between human health, livestock health and wildlife health are put in place.

Most of the new emerging infectious diseases have an animal connection e.g. SARS and bird flu. Linkages between the sectors need to be in the form of joint operational activities in research and surveillance.

Long term

1. Processes should be put in place that allow the ongoing evaluation of diagnostic technologies.

New technologies will flow from fundamental research. The capacity to evaluate these technologies and incorporate them into diagnostic laboratories is required.

2. e-health systems should be implemented strategically.

e-health systems are developed and trialed in an opportunistic manner. This needs to become more focused and strategic.

3. Wireless based connectivity for diagnostic systems should be widely deployed.

4. Personal medicine developments are linked to point-of-care diagnostics.

5. The appropriate regulatory and social support frameworks are in place for the deployment of personal diagnostic systems

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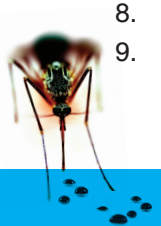

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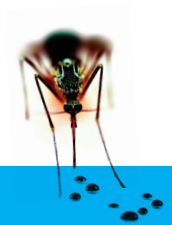

Chapter Seven: Treatments

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Introduction to Treatments

People's current attitude toward emerging infectious diseases (EID) appears to be heavily influenced by the historical fact that smallpox eradication was officially announced by the WHO in 1980[1]. It has been considered as an epoch-making success in human history. However, we should also consider other unexpected consequences of this "glorious victory" that seem to affect the policies for combating infectious diseases.

Since the eradication of smallpox was accomplished by aggressive enforcement of the worldwide vaccination program[2], a strong impression was generated that vaccines should generally serve as the most effective weapon for fighting infectious diseases. For certain infectious diseases, such as poliomyelitis and measles, it is true that the vaccine-based strategy can be successful and a large number of human lives have actually been saved. As a result, usefulness of the efforts to develop vaccine has been appreciated and emphasized – sometimes overemphasized.

This emphasis appears to have affected the mentality of most people throughout the academic, industrial and administrative sectors of our society, involving medical professionals, scientists, investors and policy makers. Meanwhile, no significant effort appears to have been made to develop therapeutic drugs that will be effective for vaccine-preventable infectious diseases. Twenty-eight years after the smallpox eradication, what we are now confronting is a threat, or at least a constant concern, of bioterrorism exploiting *Variola major*, the virus causing smallpox[3]. At the same time, we do not have even a single therapeutic intervention specifically targeted against *Variola major*.

Smallpox vaccination programs have been terminated since the eradication of the disease and yet there is a large population of unvaccinated, vulnerable people. Should smallpox re-emerge for any reason, we do not have any options for specific treatments to save those people. Similarly, no active treatment regimen is available for most other viral diseases against which prevention by vaccination is believed to be the prioritized strategy.

For example, subacute sclerosing panencephalitis caused by the measles virus is still a fatal disease with no effective treatment. In the case of flavivirus infections, such as dengue fever, many efforts have been made to develop a vaccine due to the belief that vaccination should be more cost-effective than drug treatment, which the economy of the epidemic area may not be able to afford. However, no effective vaccine is available yet. Neither is an antiviral treatment.

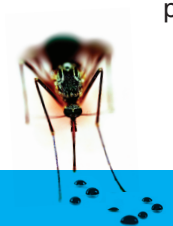
TABLE 15: CURRENTLY AVAILABLE COMBATING STRATEGIES AGAINST MAJOR VIRAL DISEASES

Disease	*Vaccine*	*Treatment*
Smallpox	+	-
Measles	+	-
HIV/AIDS	-	+
Dengue	-	-
Influenza	+	+
SARS	-	-
HPAI[a]	-	+
Novel EID	-	-

[a]Vaccine against only HAPI virus of H5N1 subtype has been developed and manufactured as a pre-pandemic vaccine.

Table 15 shows the current situation of the strategies available for combating some of the representative viral diseases. It is clear that those diseases, for which both vaccines and treatment are available, are exceptional. Although these examples may not belittle the importance of the effort toward the vaccine-based strategy against EID, they also bring up the following points:

1. For tackling the problem of EID, we should learn lessons from “EID” of two other kinds - “Eradicated Infectious Disease” (namely, smallpox) and “Existing Infectious Diseases”, such as measles and dengue fever.
2. Even for those infectious diseases for which a preventive vaccine is available, therapeutic drugs are required for more effective risk management.
3. For certain infectious diseases, the development of a preventive vaccine is extremely difficult (or maybe impossible) likely due to the unique nature of the interaction between the causative agent and human immune system.
4. Vaccines may not always be the preferred tool, because also antimicrobial drugs are emerging that can have a stronger impact in controlling the disease caused by some pathogens.



Therefore, development of treatment drugs that can inhibit growth or pathogenic mechanisms of the microorganisms constitute an indispensable component in the Roadmapping Converging Technologies to Combat EID. In this chapter, roles of treatment in relationship to the RAND EID life cycle model and the roadmap for drug development based on the result of TRM Workshops are described with policy recommendation at the end.

Roles of Treatments in Combating EID

Treatment technology has successfully contributed to the combat against a variety of infectious diseases, especially those caused by bacteria. For example, when the cause of Legionnaires' disease, which emerged in 1976, was identified as a novel bacterium, *Legionella pneumophila*, treatment with antibacterial drugs was quickly and effectively formulated. Similarly, since *Helocibacter pylori* was discovered in 1983 as a cause of chronic gastritis and gastric ulcer, treatment strategies for these diseases have dramatically changed. Elimination of the bacteria with antibacterial drugs is currently the treatment protocol of choice.

A typical example of the contribution of treatment strategy to combat viral disease can be found in the case of human immunodeficiency virus (HIV) which causes acquired immune deficiency syndrome (AIDS). Since the discovery of HIV in 1983, an enormous amount of financial investment and academic effort have been made toward HIV vaccine development, now covering a quarter of a century. For some vaccine candidates, clinical trials of various scales have also been carried out, some of which have been in APEC economies. However, results of the vaccine research and clinical trials have so far been disappointing and a successful anti-HIV vaccine, or even a potential candidate, remains unavailable. There are also controversial ethical issues that have been raised for undertaking HIV vaccine clinical trials[4]. The good news about HIV is that during the same period 1983-2008, academic and industrial efforts have also been made to develop the drugs that block HIV replication. As a result, a variety of effective anti-HIV drugs are already in clinical use, significantly improving the prognosis of HIV/AIDS patients.

Consideration of the issues associated with the HIV/AIDS pandemic may be useful for assessment of the possible impact of treatment technology on the strategy to combat EID in general. First, it is now clear that identification and detailed characterization of the pathogen does not necessarily warrant vaccine development. HIV is notorious for its frequent mutation that alters its antigenic determinants, weakening the effects of host immune response. HIV also attacks the CD4-positive T lymphocytes playing a central role in the cellular immunity and there are other viruses known to affect the human immune system. It is possible that the effects of host immunity elicited by vaccination may intrinsically be limited for those viruses.

Secondly, treatment technology can also contribute to prevention of spread of the disease (Figure 10). Successful treatment with the anti-HIV drugs can keep the viral load of the patients at a very low level if it cannot completely eliminate the virus. Epidemiological data indicate that treatment of pregnant mothers with anti-HIV drugs significantly reduces the rate of mother-to-infant transmission[5]. Treatment of HIV-related careers may also be effective for decreasing the risk of sexual transmission when use of condoms is difficult for some reason. Today, there are more than 30 millions people living with HIV/AIDS in the world and the number is still increasing. Occasionally, arguments are heard that spread of HIV/AIDS patients could have been prevented if the financial resources spent on vaccine development had been allocated for manufacturing and distributing the anti-HIV drugs. These arguments sound reasonable especially in the developing countries with large burdens of the HIV/AIDS epidemic and limited availability of anti-HIV drugs.

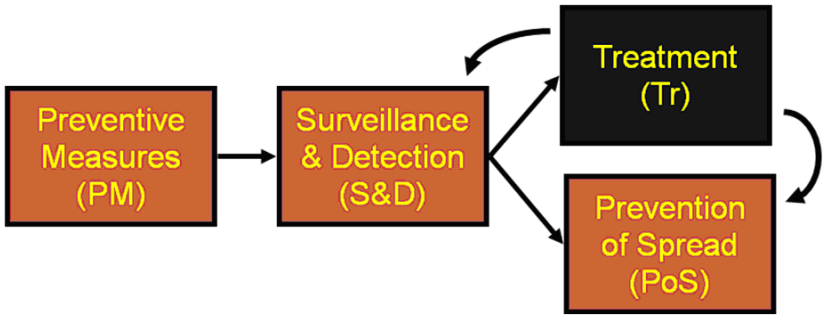
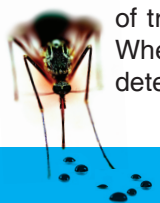


Figure 10: Roles of treatment in Combating EID (Based on RAND model)

Therefore, balanced allocation of various resources should be considered for the pathogens whose vaccine appears to be hard to develop. More emphasis could wisely be put on drug discovery for those cases.

Thirdly, availability of treatment technology could encourage the general public to take a diagnostic test. Some people are now unwilling to know if they have contracted an incurable fatal disease. Consequently, this has discouraged many persons from taking the diagnostic test. For example, people used to hesitate to take the cancer screening test because they did not know how to face the reality when they are diagnosed as having the malignant disease. Only when the treatment technology has advanced, enabling early detection of cancer so that this can lead to a successful cure, have people recognized the value of the screening test.

Similarly, the screening test for HIV now provides infected people with the opportunity to start receiving effective drug treatment earlier. In other words, it is likely that availability of treatment technology can serve as an incentive for early diagnosis of the disease. When the general public is encouraged to take the screening test, surveillance and detection of the disease may be achieved more easily and successfully (Figure 10).



In summary, treatment technology should be useful not only for rescuing the EID patients but also preventing further spread of the disease. Availability of effective treatment may also positively influence the public health measures, such as surveillance and detection.

Roadmap Discussion

TABLE 16: TECHNOLOGY ROADMAP FOR TREATMENTS

		Short term: 2007 - 2011	*Medium term: 2012 - 2016*	*Long Term: 2017 - 2020*
User's Requirement		Improvement of currently available drugs (e.g., higher efficacy; reduction of side effects; lower price; stability, etc.)	Availability of a larger variety of safe drugs with more effectiveness, more safety and more stability	Availability of stable, long-lasting, safe and affordable drugs that can be used for personalized medication
Technology	*Development*	• Identification and 3D structure analysis of pathogen molecules that serve as treatment targets • Elucidation of drug resistance mechanisms • Cell- or tissue-based assays for drug activity	**Highly competent drugs** • Bioinformatics • Accelerated and accurate method for structure-based drug design • High-throughput cell- or tissue-based drug screening and assay system	• Genomics-based molecular modeling and drug design • Tailor-made drug design for individual patients and respective pathogen strains
	Production	**Cheaper and safer manufacturing** • Implementation of QA & QC for production control • Post-marketing evaluation of drug efficacy and side effects	• Highly efficient reactors for chemical synthesis • High-speed automated production & QA/QC	• Robotics for high-speed and cost-effective tailor-made production & QA/QC • Production and packaging for cold chain-free distribution
	Delivery	**Improvement of drug delivery efficacy** • Pharmacokinetics • Pharmacodynamics	• Drug delivery targeted to specific cells or tissues • *In vivo* drug monitoring system	• Pharmacogenomics • Nanotechnology-assisted drug delivery system

Technical & socio-political Challenges	• Difficulty in pathogen protein expression and crystallization • Limited access to state-of-the-art technologies	• Difficulty in standardization of drug action mechanisms • Rapid clinical assessment of the efficacy and safety of novel drugs	• Drug-resistant pathogens with novel mechanisms
	• Low public awareness • Difficulty in information sharing • Limited source of budget	• Delays in drug approval process • Patent restriction • Limited source of budget	• Ethical issues (personal genomic information, etc.) • Socio-political and Economic barriers between nations
Activities and R&D programs	• Information exchange on pathogens and drugs • Improvement of the rationale for synthesis and purification of chemicals • Support for the patenting process • International coordination of clinical trials • Technological infrastructure (sequencing, protein chemistry, etc.)	• Core-lab facilities with state-of-the-art technologies, such as powerful sequencing, microarrays and proteomics • EID surveillance for detection and prediction of new pathogens • Improvement of bioinformatics algorithms • Lobbying for accelerated drug approval	• Multidisciplinary collaboration (e.g., biomedicine and nanotechnology) • APEC-based drug production company and regional facilities • Lobbying for international cooperation among APEC nations at the socio-political and economic levels

Table 16 summarizes the suggested technological roadmap for EID treatment. For developing treatment against EID, technologies in two aspects are necessary. One is common to drug discovery in general and the other unique to treatment of infectious diseases. Some of the important technologies for the respective aspects are discussed below.

Technologies Expected for Drug Discovery in General

A. Structure-based drug design

Application of structural biology for drug discovery is not a novel concept[6]. Modern drug discovery projects often involve the structure-based strategy in combination with the high-throughput screening (Figure 11)[7]. There are already examples in which elucidation of three dimensional (3D) structure of the protein has successfully led to development of therapeutic drugs, such as imatinib mesilate for chronic myelogenous leukemia[8] and anti-influenza virus drugs namely oseltamivir and zanamivir[9].

However, further technological development is necessary for the structure-based drug design to be more practical. Required technologies include recombinant protein expression and purification, protein crystallization, analysis of protein 3D structure and a computational method for *in silico* examination of the interaction between chemical compound and the target protein. If algorithms for molecular modeling are improved, genomics-based drug design may also be achievable.

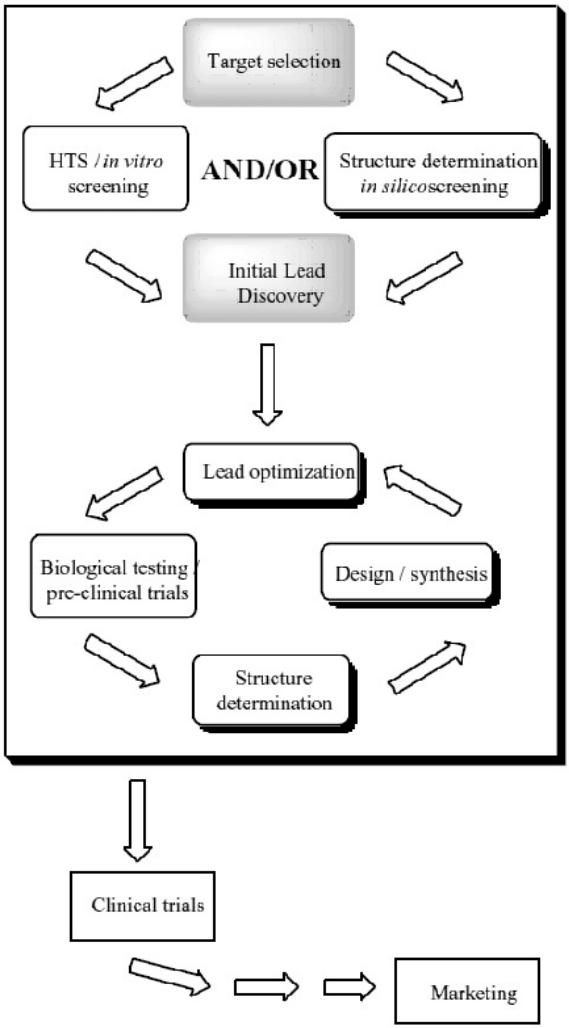


Figure 11: Relationship between Different Aspects of a Modern Drug Discovery Project

The box encompasses aspects related to basic research and pre-clinical trials which are discussed in the paper. The areas in which structural biology has traditionally contributed are within the highlighted rectangular outlines; the areas where structural biology has started to provide information in more recent years are within the rectangular outlines and shaded gray[7].

B. Nanotechnology-based drug delivery

Delivery of the drug to a specific organ, tissue or cell where it should exhibit its effect is important for successful treatment with a higher potency and a lower risk of side effects.

Recent advances in nanotechnology suggest that inclusion of a therapeutic compound in nano-particles with an appropriate surface property could show an affinity for specific target cells prior to delivery of the drug to the right target.[10]

C. Pharmacogenomics and personalized medicine

It is known that metabolism and kinetic behavior of certain drugs can significantly be different from person to person most likely due to the influence of the different genetic backgrounds of individual patients. This idea led to a novel paradigm of pharmacogenomics based on which personalized medicine is expected to be developed.[11] For the treatment of infectious disease, it is possible that interaction of the drug with the target pathogen might also be controlled by the host factor(s) encoded by the patient's gene(s). Therefore, pharmacogenomic studies should be carried out in order to investigate and elucidate the host genetic factors that determine the efficacy of infectious disease treatment. Accumulation of the data from those studies will allow us to choose right combination of the drugs and administration strategy for each patient in a tailor-made manner so that the best use of the treatment strategy can be made.

Technologies Specially Required for Combating PathogenicMicrobes

A. Rapid identification of the causative agent and genome sequencing

For structure-based drug design, genomic information of the microbe causing the disease is essential. In the early 1980s, it took as long as 2 years for identifying HIV as the cause of AIDS.[12-14] The process was faster in the case of SARS outbreak from 2002 to 2003 and the specific coronavirus responsible for the disease was identified and characterized for the entire genome nucleotide sequence within a few months.[15] It is hoped that technological advances in the fields of molecular biology, engineering and computer science may further accelerate the process in the near future. Some of the examples are described in the DIAGNOSIS chapter of this report

B. Elucidation of replication and pathogenic mechanisms of the microbes

For developing a therapeutic drug against a pathogenic microbe, it is usually effective to target the microbial proteins involved in replication or pathogenic mechanisms. Therefore, basic research for characterizing the pathogen for these aspects constitutes an integral component for developing the therapeutic intervention.

C. Comprehensive structural biology of microbial proteins

Soon after the complete nucleotide sequence of SARS coronavirus genome had been determined, systematic efforts were made to elucidate the 3D structure of the proteins encoded by the viral genome. These efforts led to an attempt to discover anti-SARS virus drugs through the structure-based strategy. For example, the chemical compound that can inhibit SARS coronavirus protease has been identified relatively quickly (Figure. 12). [16, 17]

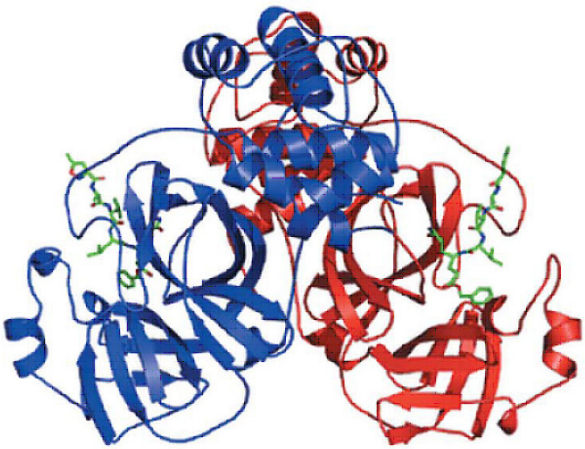


Figure 12: The three dimensional structure of SARS coronavirus protease (M^{pro}) with bound peptidomimetic ester inhibitor N3. M^{pro} monomers are colored red and blue. The inhibitors (one per monomer) are colored green17.

Currently, the rate limiting step for structure-based drug design appears to be an elucidation of the 3D structure of the microbial protein. If the 3D structures of the proteins of known microbes are comprehensively determined, the database would become a useful information source. When the causative agent of an EID is found to be closely related to a microbe of the species whose protein structures are already determined, the structure of the novel pathogen's protein that becomes treatment target may be predicted by the computational molecular modeling method based on the data of the known species.

A streamlined system, which connects identification of the pathogen causing EID, prediction of the 3D structure of the pathogen proteins with possible functional implication and computational designing of the lead compounds for therapeutic drug development will tremendously be useful

D. High throughput assay for the drug effects against the pathogen

High throughput cell-free system for measuring the effects of chemical compounds on the function of microbial protein will be for the initial screening. For reliably evaluating the therapeutic effects and toxicity of a large number of drug candidates, high throughput cell- or tissue-based assay system appropriately mimicking the *in vivo* situation of the microbial infection should be developed.

E. Rapid evaluation of drug sensitivity and solution for the drug resistance

It is known for many microbial pathogens that minor genetic changes in the pathogenic microbe could affect its sensitivity to treatment drugs. For rapid evaluation, the relationship between genetic profiles and sensitivities to different drugs needs to be systematically investigated. The compilation of the data from those studies would allow us to choose the most effective treatment strategy for each case. Elucidation of the detailed molecular basis for the drug resistance would also be useful for developing the novel drug that can overcome the resistance. Development of the drug that does not allow emergence of a resistant strain of the target pathogen would be ideal.

For these technological developments to be achieved within a reasonable period of time, sufficient levels of incentives would have to be generated from both academic and industrial points of view. In order to encourage the industrial party to actively participate in the development of the treatment technology, acceleration of drug approval process would also be helpful. However, safety issues in drug development should not be compromised. Therefore, a policy for international coordination of comprehensive clinical trials with an acceptable ethical standard should be made effective as well.

Policy Recommendations for Treatments

Short term

Promoting basic microbiology with emphasis on microbial replication and pathogenesis

Mechanisms for microbial replication and pathogenesis could be a good target for therapeutic intervention. It is therefore useful to elucidate those mechanisms in detail. A high priority should be put in a strategic manner to promote basic research to characterize pathogenic microbes in these aspects.

Promoting structural biology of microbial proteins

Progress in protein structure biology led to practical application of structure-based drug design for various diseases. In order to utilize this technology more effectively for treatment of infectious diseases, it is recommended to encourage and promote research effort directed to structure biology of microbial proteins.

Balanced allocation of funding and human resources

It is recommended to compare and evaluate different strategies for tackling individual infectious diseases based on objective scientific evidence. If the merit of the effort for developing therapeutic drug is clear, financial and human resources should be allocated accordingly.

Generating more academic and industrial incentives

In order to achieve balanced allocation of human resources, it is also important to systematically set up appropriate incentives for those who are able to contribute to the related areas of work. For basic researchers, due academic credits, such as scholarly recognition and promotion, would be a good incentive. For those who work for private companies, industrial incentives, such as a patenting right and marketing privilege, may be effective.

Medium term

Promoting computer science applicable for microbial genomics and molecular modeling

Compared with direct investigation of the higher structure of microbial proteins, molecular modeling technology based on microbial genome data is expected to be less labor-intensive and much more rapid. The computational method is likely to be more cost-effective as well. However, currently available programs generally do not achieve molecular modeling of microbial proteins with the accuracy and reliability comparable to those of the classical methods. Systematic compilation of more protein structure data will facilitate elaboration of the modeling algorithm. Improvement of the hardware used for the modeling studies will also be important. Sufficient support for these lines of effort is highly recommended.

Promoting basic and applied research in the field of nanotechnology and pharmacogenomics

Both nanotechnology and pharmacogenomics are important research fields related to administration of therapeutic drugs and their delivery to the target tissue in the body. In order to make the best use of newly developed drugs for infectious diseases, studies

of these areas should also be encouraged and promoted in a systematic and strategic manner.

International collaboration for the surveillance of drug resistant pathogens

Introduction of a new therapeutic drug that counteracts pathogenic microbes could result in emergence of strains resistant to the drug. It is highly recommended that effective surveillance system should be established for detecting drug resistant microbes at an early stage of emergence through international effort.

Long term

International coordination for ethically acceptable clinical trial programs.

When a new drug is developed, it has to be evaluated first through a due process of clinical trials before it is distributed. Technological advancement will make the drug development steps faster and a need for clinical trials will increase. Therefore, coordination of ethically acceptable clinical trail programs should be established among APEC economies.

Legislation for an accelerated approval of a safe and effective drug for EID treatment

When the drug development process becomes more efficient, it is possible that the legislation for the drug approval becomes a rate-limiting factor. In order for the drugs, which have gone through a due process of clinical trials, to be distributed to the scene of clinical practice in a timely manner, it is recommended for the legislation process to be accelerated once the safety and effectiveness of the drug is confirmed.

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Chapter Eight: Modeling and Simulation

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Introduction to Modeling and Simulation

Gene Bellinger stated in his introduction to Modeling & Simulation in "Systems Thinking: A Journey in the Realm of Systems" that:

> *"After some consideration regarding a meaningful way of putting System, Model and Simulation in an appropriate perspective I arrived at the following distinction.*
>
> - *System: A system exists and operates in time and space.*
> - *Model: A model is a simplified representation of a system at some particular point in time or space intended to promote understanding of the real system.*
> - *Simulation: A simulation is the manipulation of a model in such a way that it operates on time or space to compress it, thus enabling one to perceive the interactions that would not otherwise be apparent because of their separation in time or space.*
>
> *Modeling and Simulation is a discipline for developing a level of understanding of the interaction of the parts of a system, and of the system as a whole. The level of understanding which may be developed via this discipline is seldom achievable via any other discipline.*
>
> *A system is understood to be an entity which maintains its existence through the interaction of its parts. A model is a simplified representation of the actual system intended to promote understanding. Whether a model is a good model or not depends on the extent to which it promotes understanding. Since all models are simplifications of reality there is always a trade-off as to what level of detail is included in the model. If too little detail is included in the model one runs the risk of missing relevant interactions and the resultant model does not promote understanding. If too much detail is included in the model the model may*

> *become overly complicated and actually preclude the development of understanding. One simply cannot develop all models in the context of the entire universe, of course unless you name is Carl Sagan.*
>
> *A simulation generally refers to a computerized version of the model which is run over time to study the implications of the defined interactions. Simulations are generally iterative in there development. One develops a model, simulates it, learns from the simulation, revises the model, and continues the iterations until an adequate level of understanding is developed."* [1]

Following the above quote, modeling and simulation (M+S) are another approach to help solving real and meaningful problems. Computer simulation increases understanding of the problems and how the objects of interest behave under certain conditions. It also helps to analyze what would have been incomprehensible otherwise and to determine control parameters with desirable outcome. In some cases, M+S also provides ability to determine how systems will perform under a variety of conditions.

Computer simulations are used in many aspects. Examples are weather forecasting, aircraft design, flight simulators, molecular drug design, traffic simulation, etc.

The science behind computer simulation is "computational science" or "scientific computing". It is a field of study concerned with constructing mathematical models and numerical solution techniques by using computers to analyze and solve scientific, social scientific and engineering problems. "Computational science" is more related to solving problems and it is different from "computer science".

From a scientific point of view, computational science (and M+S) offers another approach in addition to the conventional "theory" and "experiment" approaches. It rapidly has become more widely adopted in the scientific community. It allows us to prove the feasibility of concepts, theories or experimental elements. M+S also helps us to understand phenomena and construct concepts or theory from data that are characterized by a lack of understanding. In other words, M+S allows us to perform virtual experiments that would be impossible or unaffordable to set up in reality.

The continuously improving processes of performing the simulation are

- Data input management
- Mathematical Model construction
- Programming and Processing
- Data Output management
- Interpretation

Current Stage of Computer Simulation

Computer Simulation can be performed in a scale ranging from a laptop computer or on hundreds of thousand CPUs system. This depends on the designed software and complexity of model, as well as pools of resources that one can reach. Such resources include hard infrastructures such as High Performance Computing (HPC) and networking facilities, as well as soft infrastructures such as data, connectivity, policy and people. Recently, Grid Technology became more popular. It aims to build the infrastructure for a global virtual environment such that resources can be shared virtually across geographical space regardless of displacement and problem size, which can be readily scaled.

Computer graphics are commonly used to display results of a computer simulation. Simulation results are often aggregated into static images using various ways of scientific visualization. Animations can be used to visualise a simulation in real-time e.g. in training simulations. In some cases, animations may be useful in faster than real-time or even slower than real-time modes. In addition, GIS analysis and spatial visualization of multi-dimensional data over maps is becoming very common and very useful today.

Despite varieties of its practical usage and its success, M+S is limited to problems that are well-defined in scope and known range of inputs, for example, design process of automobiles industry or air-craft. M+S can save the industries time and billions of dollars. However, M+S can address only those scenarios that are align with predefined assumptions. In molecular drug designs, it may show insight into the molecular level, but may not yet be able to indicate how the new synthetic drugs could affect each patient. Moreover, it will require weeks or months to process.

This limitation can be attributed to two major factors:

- The first factor is the non-uniform infrastructure as mentioned above.
- The second factor is more difficult. In order to have a model that is very complex to describe the real scenario, the knowledge required will be highly multidisciplinary. This will either require a very knowledgeable expert who knows many fields of expertise, or this will need a team of many experts to work together. Neither of these approaches is straightforward to build. However, the good news is that M+S is now a well accepted emerging trend of the scientific advancement and steady improvements in capacity are expected.

Future of Computer Simulation

According to the two major difficulties, the strong growth of the ubiquitous computational environment is the pro-factor that supports the rapid advancement of computer

simulation infrastructures. In 10 years, a laptop will reach the teraflops computing power of the server system that cost tens of thousand US dollars today. Appliances and your belongings can have their own network IP addresses. New paradigm of HPC will be very different and more powerful and less energy consumptive than today. However, what you cannot count on is the human element and acceptance of the new capacities that M+S can offer.

From a perspective which understands converging technology, scientists and many people in general accept that our daily life and the world are facing problems that no one can manage them all alone. From more global connectivity, we will learn about many new avenues of computational applications and have much more information to process. Then our collective knowledge and understanding will be expanded. More multidisciplinary teams will be able to grow, learn and practice providing answers to complex problems, advice on decisions, risk assessments of everyday actions etc. However, we are in tremendous pressure against time. Natural disasters, energy shortage, climate change and EID are factors that generate immediate consequences for people's lives.

In practice, the author believes that we will be in the imaginable futures, which have robust networks of real time data and computing resources applicable to all major global problem areas. Simulations will be performed with shared resources, including the laptop and cell phone – personal computer in your hand. The form of computer simulation usage will be application-centric as operations through internet base portals become available with shared virtual engines behind the scene. More and more applications will become available in such a manner.

Roles of Modeling and Simulation in Combating EID

From the series of APEC-EID workshops, the explicit needs of computer simulation became most visible only in the later events of the series. For example, "molecular modeling" can help in designing new vaccines or developing vaccine delivery systems. Another example, data available from a tracking and monitoring system could be mined and analyzed to create a mathematical or statistical model to forecast outbreaks of a disease. One of the suggested approaches is the "InfluSim"[2] which is a pandemic disease planning tool available as a web portal for a variety of diseases.

The ideal goal of M+S for EID is to achieve an effective whole system model. In that instance the model should provide quantitative decision support analysis in the manner of robust scenario based options. The model will be extremely complex, since it will not only consider the physical aspect of the disease, but also include social and economic factors which are hard to quantify and incorporate into the calculation. The technical approach to construct this will be multidisciplinary by nature. The key technology development factors will be:

- “Data mining and advanced mathematics”
- “Data visualization”
- “Data integration and interoperability”
- “Ubiquitous computing infrastructure and e-Science”

All of the above will have to deal with the enormous size of the multi-dimensional data sets. However, the larger hurdles will be the non-technical problems which are delicate because they involve human factors and interfaces. According to the EID lifecycle model (presented by RAND) and the key technologies that impact on each period of the model, computer simulation can briefly related to other components as follows.

Ubiquitous Computing

From M+S point of view, ubiquitous computing will act as fabric of infrastructure for modeling and simulation in EID applications.

- Real time inputs
- Information/knowledge sharing/integration
- Processing power
- Fast adapting solutions
- Visualization
- Collaboration

Preventive measures

M+S can help predetermine the most likely situations according to changing risk factors before these actually happen, by developing a variety of plausible situations e.g.:

- Conditional scenario assumptions and story lines planning,
- Pre-determined mutations of EID,
- Shorter times for vaccine development (technical view, not clinical),
- Bioinformatics projections.

Surveillance and detection

- Anomaly pattern extraction,
- Conditional models from early signs of warning parameter

Treatment

- Molecular Dynamics M+S Drugs design molecular interaction System
- Effect of drugs on pathogens
- Effect of drugs on environment
- Effect of drugs on organs

- Effect of drugs on organism
- Virtual screening
- Vaccine/Drug Delivery method

Prevention of Spread

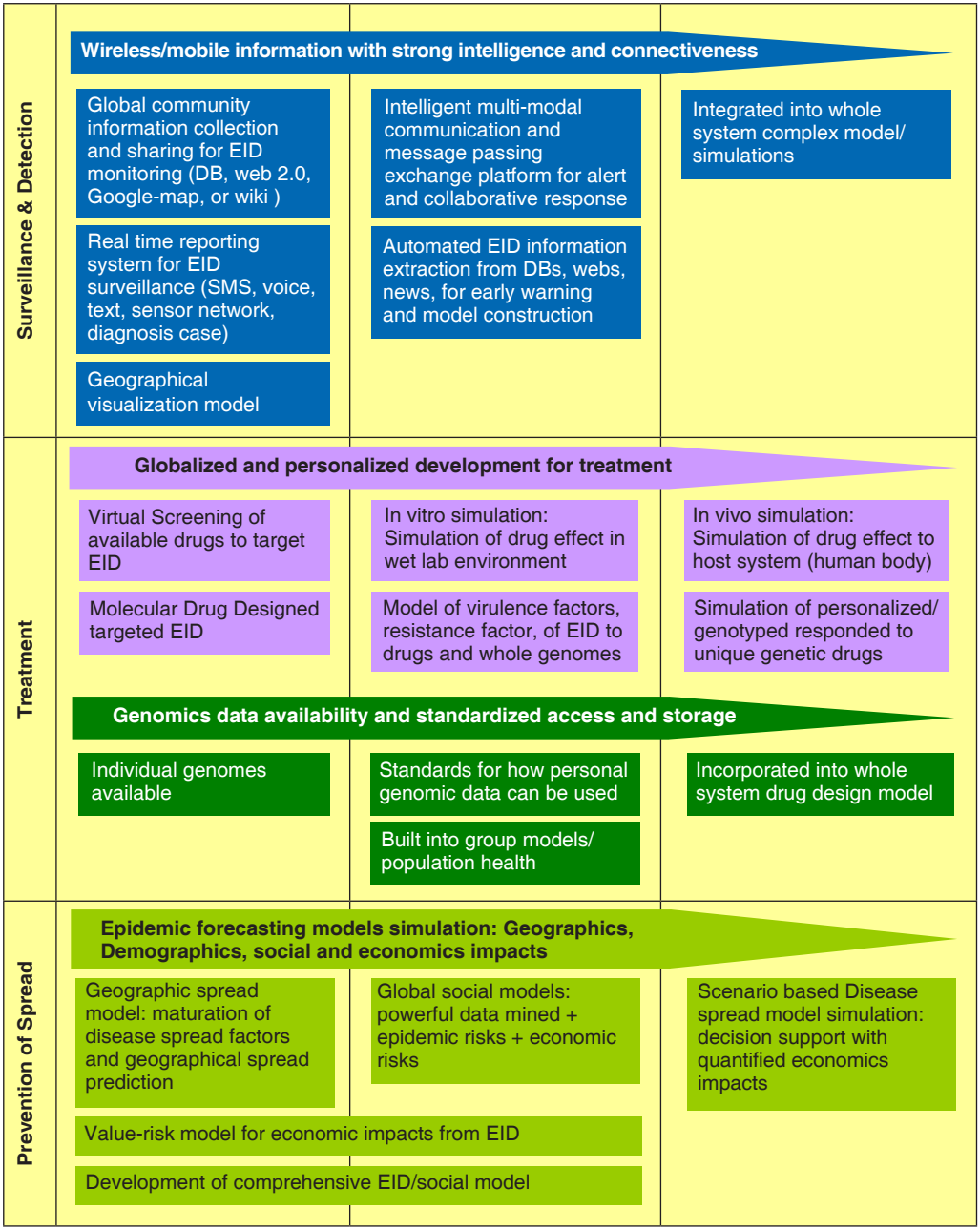
- Spread model
- Epidemic coverage scenario
- Devise counter attack effectiveness options

Roadmap Discussion

Table 17 represents M+S Roadmap. The roadmap was drawn according to the EID Life Cycle in Figure 3 and summary gather from a series of workshops, under an APEC-Wide Foresight Project[3-6].

Table 17: Technology Roadmap for M+S

	Short term: 2007-2011	Medium term: 2012-2016	Long term 2017-2021
User Requirement	Quantitative or comprehensive presentation of threat of pandemics Needs to Reform of system of alerts detection	Effective global traceability Minimizing Social/business lost Effective global traceability from EID	Understandings and Management of EID with respect to climate changes, rapid land use and social structure changes
Preventive Measure	Data mining and data visualization Global analysis, reports, and data sharing Disease Data warehouse and Data mining tools	Geographical data and historical data visualization with global network links Early warning signals data mining model	Part of a whole system model of risk/evolution of bio-phenomena (includes mutation risks + vectors behavior changes)


Surveillance & Detection
Wireless/mobile information with strong intelligence and connectiveness
Global community information collection and sharing for EID monitoring (DB, web 2.0, Google-map, or wiki)
Real time reporting system for EID surveillance (SMS, voice, text, sensor network, diagnosis case)
Geographical visualization model
Intelligent multi-modal communication and message passing exchange platform for alert and collaborative response
Automated EID information extraction from DBs, webs, news, for early warning and model construction
Integrated into whole system complex model/ simulations
Treatment
Globalized and personalized development for treatment
Virtual Screening of available drugs to target EID
Molecular Drug Designed targeted EID
In vitro simulation: Simulation of drug effect in wet lab environment
Model of virulence factors, resistance factor, of EID to drugs and whole genomes
In vivo simulation: Simulation of drug effect to host system (human body)
Simulation of personalized/ genotyped responded to unique genetic drugs
Genomics data availability and standardized access and storage
Individual genomes available
Standards for how personal genomic data can be used
Built into group models/ population health
Incorporated into whole system drug design model
Prevention of Spread
Epidemic forecasting models simulation: Geographics, Demographics, social and economics impacts
Geographic spread model: maturation of disease spread factors and geographical spread prediction
Global social models: powerful data mined + epidemic risks + economic risks
Scenario based Disease spread model simulation: decision support with quantified economics impacts
Value-risk model for economic impacts from EID
Development of comprehensive EID/social model

In preventive measure, key developments are to understand the diseases as much as possible. That includes understanding their dependency on surrounding environment. The M+S contribution are the derivation model that will provide us indices which are the early warning signals from enormous collected data, information and knowledge. Milestones to be achieved are to have disease data warehouse with globally shared reports. Analysis tools, even incomplete, must be developed and integrated into a larger picture of the whole system.

The change of lifestyle in the ubiquitous environment reflects the growth of social network information and unstructured data. Future surveillance and detection dependent on

social network information will be as important as formal reporting systems. Seamless information sharing and integration are crucial. Information extractions from vast varieties of information are the key development ability. Milestones to be achieved are real time reporting systems, with valuable message exchange through multi-modal communication. Integration of social and semantic web with information extraction feature is expected. This will be a part of a larger and complex system.

In treatment, key developments are the continuously growth of drug simulation from virtual screening towards the drug effect to the host. Milestones to achieve are the capacity to simulate with acceptable accuracy, meaningful interpretation and practical speed up of the more and more complex models.

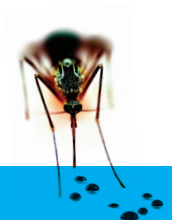
In prevention of spread, key developments are the expanding scopes of the epidemic forecasting. Milestones to achieve are the models themselves which can gradually reflect simulation output towards physical and geographical outcome and social and economics impact.

Key messages for R&D programs are to continue building sustainable and reliable cyber-infrastructure, support interoperability and strengthen platforms for multi-disciplinary R&D. Grow venues for cross-discipline people to interact and exchange value effectively. Invest in e-science research.

Policy Recommendations for M+S

Table 18: Policy Recommendations for M+S

Policy Actions	*Short Term: 2007 - 2011*	*Medium Term: 2012 - 2016*	*Long Term: 2017 - 2021*
Technology			
Establishing EID network (and other coordinating response to emergency network)	• Crucial and relevant message exchange among member agencies • Multi-mode communication (IP, RF, etc)	• Action aware and process coordination among agencies • Include information extraction from social network	• Optimized coordinating effort aware with logistic optimization model • Multi-lingual communication



Cyber-infrastructure for EID networks: • Network • Telecomm • Sensor • HPC • Security • Availability	Connecting: • Continent • Regional hub • Major cities • Major hospitals • Health departments	• Rural areas • Provincial hospitals • Public health units	• Last mile • local community centers • households
Invest in R&D program in multi-disciplinary science for EID applications: Computational science and engineering, Data Mining, Grid applications, E-Science, Earth Science, remote sensing, genomics, Bio-informatics, Sensor network, Social behavior, Computational Economics , Computational linguistics.	Targeting: • Early warning sign detection • Drugs screening	Targeting • Physical scenario impact prediction	Targeting • Social/economic impact prediction • anticipated counter response scenario prediction • Fast and trustworthy drug design ability
HRD and Public Information			
Education and training program for multidisciplinary science and profession to work as a team or virtual team.	• Setting team qualification and expertise • Set target number • Create curriculum in formal or informal education	• Create new career opportunity • Recruit • expand	• Maintain equilibrium professional networks
Invest in international HR-EID collaborative program. Create enough knowledge EID-HR that actions can be distributed and decentralized	• Report and surveillance information network	• Coordinating actions in national scale	• Coordinating actions in local community scale

Create Social network forum that attract EID event reporting globally.	• Information sharing, with monitoring and event tracking purpose	• Information extraction that can lead to early warning sign or pattern	• Feed back channel to share and structure the fight against EID
Using visualization and virtual gaming simulation in EID awareness and social educating program to create public awareness, understandings and public participation.	• Apply 2nd Life or virtual society for EID social study purpose • Using real time monitoring and tracking information.	• Using extracted information and forecast trajectory scenario from simulation model.	• Anticipate human interaction to project possible scenario and study response
Regulation and Organization			
Form coordinating Organization for EID networks (and other coordinating response to emergency network)	• Hosting national and/or regional EID networks • Virtual lab type of infrastructure where collaboration can be done with less conflict of interest	• Expand or linking to continental scale	• Integrated global EID network
Improve acceptance level and include the result of simulation modeling into a Decision Support System along on the progress of the technology maturity.	• As another input for consideration.	• As solution options	• As action procedure guide
APEC Coordinating office for managing economic impacts from EID and other disaster	• Coordinate and align effort in APEC countries member to build competency in combating EID	• Evaluate and provide impact scenario of EID to APEC economies and UN	• Devise and share mechanism to cope with economic impact from EID
Reducing the conflict of interests in: • Social vs. commerce • Survival vs. national securities	• Specific Drugs de-regulation	• Shared technology and knowledge in specific EID domain	• Standard international protocols for EID

Public information	• PR in educating public of good practice for preventing EID • Visualization of scenario base to create awareness and expected outcome with and without their contribution • Provide information in a visual base that will communicate with public • Social network Forum that use people as monitoring inputs observation source of data input		

Table 18 illustrates conclusions drawn from the series of APEC-Wide Foresight Project workshop. The recommendations were developed upon 3 categories which are technology & HRD, public information and Regulation & organization.

In addition to R&D programs recommended earlier, APEC may consider to support the use of technology that enables tangible output through virtual collaboration such as virtual lab. Some had gone to the length to suggest that APEC may consider forming one.

In HRD policy, the "people collaboration network" is frequently mentioned throughout the series of workshop. Converging technology is through effective converging people. That is also true in general scientific community and movement of social lifestyles. APEC should also consider the new social behaviour in cyberspace as another new and effective mean to convey and communicate the information to general public.

In regulation & organization, APEC should study extensively to identify the conflicting regulations that can prohibit the regional collaborating effort to combat EID. Evaluation and estimation of social and economic impact resulting from EID crisis scenario should be performed. The international coordinating office for the purpose is also an option.

Remarks on Challenges

1. The reliability and people involve in computer simulations are the key success factors to gain general acceptance of incorporating the approach into a real world process. However, simulation has its limitations by nature. Modeling is a simplified version

of the real system. Therefore, it will never be 100% "accurate". In addition, it is important to avoid "garbage in, garbage out" situation, which is the general rule of thumb when performing M+S.

2. Another important aspect of computer simulations is the reproducibility of the results. When human behaviour becomes a part of the simulation, it will influence outcomes such that the result may not be reproducible.
3. While M+S can produce valuable options for decision support, by itself it serves at best the most likely scenario. When there are no complex and practical processes and dependencies to translate options into action in a due timely manner, M+S can become more or less useless.
4. Data mining techniques, while still being continually improved in algorithms by R&D, require a lot of data collection and manipulation. Without extensive data, it is hardly to recognize the meaningful patterns or relationships that the model will rely on.
5. Policy may also be a source of conflict of interest. Ranging from information sharing, resource sharing, national security issues, clinical trial periods, commercial values, etc., differing policy values and priorities can conflict with each other and create havoc for M+S, since the primary motivations cannot be readily specified.
6. Human collaboration will become the most critical success factor. That is also the most difficult and time consuming to establish and maintain.
7. With enormous data being produced - now exponentially - more resources will have to be allocated to information management. The most troubling problem facing today is "data cleansing".
8. The rapidly evolving computing environment can be very beneficial to enhancing the power of simulation models. The price of technology is dramatically decreasing but unfortunately, the number of people who can keep up with utilizing this new technology is insufficient to realize the full benefits.

Concluding Remarks

The ultimate requirement of M+S is to understand and able to provide realistic solutions to the EID situation globally. The so called "whole system model" has to deal with many more factors than just the disease itself. Other relevant factors, for example, are weather condition, land use, social structure, economic impacts, logistics and so on. The computational model and computer simulation provide us an approach to perform what we cannot achieve in reality. Unfortunately, the limitation in current state of technology still prevents it from being used effectively in real time combating EID when input data are changing rapidly and incomplete. Nonetheless, it is very useful for providing planning support to policy and decision makers today. The expansion of ubiquitous computing network plays the crucial role of infrastructure for all key technology components mentioned in this report especially M+S. For M+S to grow and achieve the goal it set forth, it is going through evolution process as many other converging

technologies in many new areas which were expected to have great economic impacts[7]. The early preparation of the assembly of economies such as APEC to realize and wisely utilize them will greatly enhance the chance of success in combating EID in timely fashion.

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Chapter Nine: Tracking

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Introduction to Tracking

Object tracking is a simple concept yet plays crucial roles in highly effective prevention, detection and surveillance of emerging infectious diseases (EID). In year 2002, SARS (Severe Acute Respiratory Syndrome) broke out in South China and spread to more than twenty-five countries in the world resulting in 774 deaths among 8097 cases. The disease mainly spread globally via plane traveller and was controlled through the use of quarantine, including home quarantine. Over 1,200 people were under quarantine in Hong Kong, China, 977 people in Singapore and 1,147 people in Chinese Taipei. The Singapore government amended the Infectious Disease Act to introduce the possibility of affixing offenders who break home quarantine with electronic wrist tags to keep track record.[1]

In case of Avian Influenza, the World Health Organization (WHO) is developing an electronic system to track influenza viruses through the Global Influenza Surveillance Network (GISN). The data circulated in the network contains the majority of viruses and clinical specimens including H5N1 viruses.[2]

More than 70 percent of the emerging infectious diseases are believed to be caused by diseases of animal origin so called “zoonotic diseases.” Animals are vectors of “Zoonotic Emerging Infections Diseases” (ZEIDs). For instance, mosquitoes spread vector-borne Dengue hemorrhagic fever and West Nile Virus disease; ticks spread vector- borne Tularemia and etc. Reservoir hosts of those diseases also play an important role in spreading of ZEID such as SARS spread by the reservoir host, civets; and Hepatitis E spread by the reservoir host, swines.

The epidemic of these emerging infectious diseases has tremendous negative impact on world economy and social welfare. Object tracking is part of strategic multi-national infrastructures providing tools to cope with emerging infectious diseases with an ultimate goal of ability to forecast the emergence of infectious diseases.

Trends and Needs

The demand for tracking information continues to rise with increasing complexity. The information has to be more accurate, securely and easily accessible at anytime, correctly analyzed with suggested responses or with early warning of possible threats. As the tracking infrastructure becomes more developed, integrated and automated, the amount of generated information will be enormous and requires proper handling.

The rapid pace of information technology development will help to drive down the cost of building a tracking infrastructure and make the realization of the demanded information possible. Ubiquitous computing technology will greatly improve the ability to track an object with high accuracy. The advancement in miniaturizing computing devices will allow new ways of embedding or attaching a tag to an object while more computing power and more storage in the devices allow more information about the object to be analyzed real-time and stored with greater accuracy.

With the improvement of disease detection techniques and advancement of computer modeling technologies, object tracking can be performed with greater efficiency by allocating limited resources to track an object or monitor and area according to calculated risks.

In addition to build tracking capability, countries around the world create laws and regulations to ensure well-being of their citizens. For instance, standards on food labeling and food traceability are imposed to curb the food-related disease incidents; laws and regulations on immigration and quarantine are created to deal with various infectious diseases.

Object Tracking Technologies

There are many existing systems that are capable of tracking objects. The most basic system is paper-and-pencil registration, in which an object has to be registered with required information by filling out a form. Most countries track the movements of the people and animals within the countries this way, while cross-border movements are tracked by immigration systems. Cellular phone networks can be used to locate a mobile phone in the systems. Satellite telemetry systems can locate a signal transmitter attached to a wild animal.

All the tracking systems have one thing in common. They require two main ingredients: unique object identification and object localization. The unique object identification allows a tracking system to distinguish different objects while object localization allows a tracking system to locate an object with certain accuracy.

Identification Techniques

Objects may be identified individually or in group. In a certain environment or situation, an object is needed to be identified individually as can be seen in a passport issuing system. A passport has a unique identifier associated with it so that a passport holder can be uniquely identified given the identifier. An individual may however carry more than one passport; hence, he/she may be associated with more than one distinct identifier.

Identifying objects in group can be found in logistics applications, where different homogenous or non-homogenous objects are combined to make a transport unit. The transport unit must then be given a unique identifier. In an application, a unit identifier must be unique within the system, i.e., different units are not allowed to use the same identifier.

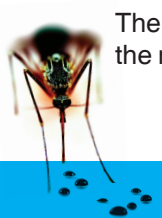
There are several object identification techniques currently in use such as number assignment, token assignment, physical characterization and biological characterization.

- ***Number assignment*** The most widely used identification technique probably is number assignment as used in passports, national identification schemes, telephone numbering systems, house registration and vehicle registration. The identifying numbers may have inherent meaning or not, depending on the requirements.
- ***Physical characterization*** The physical characterization technique, we use the different in physical description of an object to distinguish one object from others. We can find physical characterization used in the toll-way system where the toll is collected according to types of vehicles.
- ***Biological characterization*** Biological distinction can also be used to identify different objects. Today biometric technologies use fingerprint, palm print, facial features, retina, iris and DNA to identify individual biological object.

The identity of an object may be acquired by several methods such as electrical signalling, visual observation, radio communication and chemical reaction.

For added security, object authentication or verification can be implemented along with object identification to make sure that the object of interest is really what it claims to be.

Localization Technologies



There are existing infrastructures that could be utilized for tracking purposes. One of the most well-known localization systems is the Global Positioning System (GPS) that is

based on triangulation technique, in which distances from at least three GPS satellites are calculated to determine the position of an object. The same technique allows a mobile phone to be located based on the distances from at least three base stations.[3]

Apart from the triangulation technique, a position of an object can be estimated based on scene analysis and proximity techniques. In the scene analysis, an object is identified and extracted from an image and its location is estimated based on the information about the location of the surroundings. The proximity technique estimates a location of an object based on the knowledge of its proximity to a known location.[4] These techniques are often used with existing infrastructure such as CCTV networks and Wireless LAN, respectively.

An Object Tracking System

An object tracking system integrates identification, localization and data management technologies to keep track of objects in the system. The system typically consists of a tagging device, a data capture device or network, a data processing unit for management of the captured data. The tagging device is normally attached to an object of interest. It normally contains a unique identifier; however, it can also be used to acquire real-time data about the object or the surrounding environment through sensors or its current location through a positioning device such as a GPS device.

The data capture device or network of devices communicate with the tag and obtain information from the tag. The data is then sent to central processing unit for further manipulation.

There are also other types of tracking systems. There is one based on a network of CCTV cameras, where an object is video recorded. Mobile phone networks can also be used to track mobile phone users.

The integration of converging technologies is the key to successful tracking.

Object Tracking for Emerging Infectious Diseases

Understanding the role of vectors in transmission and spread of EIDs as well as human-animal interface are very essential for appropriate prevention and control of the diseases. In a study of Avian Influenza H5N1 outbreak, the wild birds suspected of being a vector migrate without boundary. The understanding of their flyway would help to prove their relationship with HPAI H5N1 and the transmission path whether it is direct to human or through poultry. Satellite telemetry was selected for tracking the birds because of the accuracy of the technology and the ability to track the birds' movement without border. This technology was modified from military surveillance system using GPS and satellites which provide accurate localization.

Overlaid on a GIS map can be the information of bird flyway obtained from the satellite telemetry system together with other factors in consideration such as AI outbreak in human, poultry, duck and etc.; or meteorological data such as temperature humidity rain water-level and etc. Visualizing and mining the data are very powerful tools to understand EID.

Roles of Tracking in Combating EID

Ability to track an object is becoming a necessity. In the EID lifecycle model, object tracking provide a supporting tool for disease prevention, surveillance, detection and prevention of spread.

Preventive Measures against EID

An infectious disease originates from the initial infection of the pathogen from a host or surround environment; hence, many preventive measures focus on minimizing the chance of the initial infection. A good number of infectious diseases emerge from the transfer of pathogen from animal to human. In preventing such diseases, we need to understand the lifecycle of the animal host and how the disease-causing pathogen is transferred from animal to human.

An animal tracking system could provide a set of tools necessary for research scientists to study of infectious diseases. The tag attached to an animal could identify and localize the animal. Added sensors could report the animal body temperature or other parameters of interest. The collected data could be analyzed to understand the cause of the initial infection. Once it is known, host animals could be tracked to prevent the infection.

Surveillance and Detection of EID

The surveillance of EID may involve monitoring of several objects or events including movements of animals and humans, deaths of animals, number of patients with similar symptoms and weather forecasts; the selection of parameters to monitor depends on potential causes of the disease. Data available from a tracking and monitoring system could be mined and analyzed to create a mathematical or statistical model to forecast outbreaks of the disease.

Graphical representation of the tracking information overlaid on geological map could provide insights into the nature of the disease.

Since the EID vectors could be either domesticated or wildlife animals which vary in high diversity, broad range of sizes, habitat behaviours and other biological features cause difficulties in identification and monitoring of these vectors in term of diseases

status and labelling of the positive animal. Current implementation of identification techniques ranging from conventional one such as visual marking to modern technology using inject-able RFID tags have been applied to those vectors. Others devices such as sensors and GPS receivers could be attached to the tags to monitor the parameter of interest that may lead to an emergence of a disease.

Prevention of Spread

In the case of a disease outbreak, quarantine procedures are normally implemented. The number of objects under quarantine might be large as in the case of SARS, where all air travellers from certain destinations must be quarantined.[5] Therefore, the issue related to limited quarantine space arose and the people had to be quarantined at home. In this situation where people need to be tracked and monitored, a tracking system would help automate data collection, reducing manpower and human errors.

Roadmap Discussion

The ultimate goal of the roadmap is to collaboratively develop networks of tracking systems that allows timely handling of emerging infectious diseases and forecasting possible outbreaks of a disease. Tracking systems, although exist in several forms and places around the world, are neither well integrated nor well equipped with data capture network. We are still on the road to develop more powerful and integrated tracking system that can provide easy and secure access to accurate and useful information on tracked objects. In order to efficiently build such system, we need to formulate a roadmap, identify challenges and join forces in coordinating research and development efforts to overcome the challenges.

The roadmap has been formulated in response to users' requirements gathered from the representatives of APEC members. During the next 2-3 years, an emerging infectious disease network should exist to facilitate data handling including collection, analysis and exchange. In the 4-6 years time, the emerging infectious disease network should have real-time tracking capability and incorporate health-monitoring features. In the 7 – 10 years time, small and cheap tracking and monitoring devices will help extending the capacity of the network to track and monitor any object of interest at low costs. With these requirements in mind, a roadmap discuss below has been drawn up.

Technology Roadmap for Tracking EID

As the main technology components of a tracking system consist of identification, localization and detection technologies, the technology roadmap below, Table 19, covers the three technology areas.

Table 19: Technology Roadmap for Tracking

		Short Term: 2007-2011	Medium Term: 2012-2016	Long Term: 2017-2021
User's Requirement		Emerging infectious disease network	Real-time tracking and health monitoring systems	Small and cheap tracking and monitoring devices
Technology	Identification	**Integrated identification** Ink tattoo, barcode, RFID, radio telemetry, Image-based identification	Mobile phone, biometrics **Small and Cheap identification with sensors** Microchip with sensors for specific diseases	Small and cheap microchip with sensors for specific diseases
	Localization	**Improved accuracy** • transaction-based: electronic payment system, transportation system, registration system • satellite telemetry	• mobile phone system • satellite telemetry	• Military-precision GPS
	Detection	**Rapid, easy, reliable detection** Backpack lab	**Cheap detection** Implantable biosensor transmitter	**Continuous microbial monitoring** **Vector migration study**
Challenges Technical & Political		• Standardization of animal RFID • Common system for collecting and analyzing data • Environmental friendly small and durable batteries • Use of biochemical energy source	• World common mobile system • Develop specific enzyme or protein marker for EID • Cellular level bio-chemical energy converter • Tag sensor accuracy and cost • Down-sized telemetry devices, cross-bordered localization	• Alternative magnetic materials or nano-technology to make light and small antenna • Systematic surveillance of vector based on research network
		• Permission to collect personal data	• Permission to collect human physiological data	

Activities and R&D Programs	• Invisible fence for EID suspect quarantine • Government funded wildlife capture and RFID tracking • Full implementation of International Health Regulation 2005	• Government or human rights committee support for collecting human physiological data • Government provides incentives for legal immigrants to use trackable mobile phone in exchange of social welfare	Vector migration study Human vital sign sensors

• Identification

For the short to medium term, the focus of technology development should be put on the integration of existing identification technologies. After the experience from the integration, the development of small and cheap sensors with identification will be very important in the medium to long term.

The integration of existing identification technologies is urgently in need because it can be done faster than developing new technologies. Furthermore, the existing identification and tracking infrastructures together with the associate information and archive could be leveraged without much added cost.

The existing systems of identifying animals with ink tattoo, barcode, two-dimensional symbol, RFID tag and satellite telemetry rely on different data capturing devices. Examining ink tattoo, bar code and two-dimensional symbol requires visual inspection while interrogating RFID tag and satellite telemetry devices requires radio communication. The challenge lies in interfacing the data capturing networks with a data processing center so that the needed data can seamlessly flows from any data capturing network to the data processing center be recognized and handled without a glitch. The hardware interfaces should be abstracted and standardized, types, security levels and formats of the data in the network need to be agreed upon.

The choice of identification techniques to be integrated should be made based on the types of objects to be tracked or monitored and the information to be collected. It will affect the equipment and process.

For medium to long term, the development of small and cheap sensors with identification will be needed so that more objects can be tracked at low costs. The sensory part of the tag is used to acquire disease-specific data from the tagged object or the surrounding environment. Tags should be small compared to the tagged objects in order not to interfere with normal behaviour of the tagged objects. The tag-packaging materials should be non-toxic and durable. In case a battery is needed, it should be small, light in weight and environmental friendly.

• Localization

The ultimate short-to-long-term goal of localization technology is the high-accuracy positioning. The localization of an object needs a supporting infrastructure to provide information necessary for position calculation. The existing infrastructures that can be used for localization are global satellite networks such as GPS and Galileo designed for general positioning; Argos system designed for collecting, processing and disseminating environmental data. Mobile phone networks such as GSM can also be used for locating mobile phones. Wireless LAN routers and RFID reader network are researched as tools for localization of WLAN clients and RFID tags, respectively. The system has their own advantages and disadvantages; for instance, GPS works very well in finding an object that is outside with direct communication with the GPS satellites. Once the direct communication is interfered, the position of the object cannot be accurately calculated. For indoor localization, either wireless LAN access points or RFID readers would provide position information with improved accuracy.

Research works related to localization mainly focus on improving the accuracy of the calculated position given available information from localization infrastructure as this would help the authority pinpoint the tracked objects reducing search time. The positioning accuracy could be enhanced through combining existing technologies, inventing new technologies or extending and building new infrastructure.

• Detection

The early detection of emerging infectious diseases is very crucial in containing damages. A rapid, easy-to-use and reliable detection kit is urgently needed in the short term so that an infectious disease can be quickly detected at its outbreak. A backpack detection kit would make health field officers work more efficiently. In the medium term, cheaper detection technology, especially implantable bio-sensor transmitter, should be developed to allow extensive coverage of detection domain.

In the long run, continuous microbial monitoring and vector migration studying should be carried out to improve global readiness to combat emerging or re-emerging infectious diseases.

Tracking Challenges

Major challenges expected to face as we try to follow the technology roadmap are creating and adopting of standards; researching and developing technologies for disease detection, device miniaturization, energy management and sensors; and operating the tracking systems.

The converging nature of the technology roadmap calls for standardization of software, hardware, information content, procedure and processes to produce automated tracking systems. The standard adoption is the most challenging part of multi-national standardization due to not only the differences in standardization-process, but also other differences such as cultural differences.

The research and development of technologies must be sufficiently funded and collaboratively carried out so that the research outputs can be built on top of the previous works.

From the stage of technology research and development to the operation of tracking systems, there might be exchange of experts, knowledge, experiment samples, etc. If not given a special treatment, the exchange might encounter difficulties causing delay in the roadmap progress. Furthermore, the tracking systems require collecting and exchanging personal data; therefore, the privacy issues must be thoroughly studied and discussed among participating members.

Activities and R&D Programs

In order to overcome the challenges, resources should be allocated to activities and R&D programs tailored to the technology roadmap.

R&D with partnership programs focusing on identification, localization and detection technologies should be initiated to provide multi-national co-ordination supporting activities such as sharing of information, education and training, standardization, standard compliance, developing laws and regulations. Exchange of experts will further help improve the information flow in the region.

Policy Recommendations for Tracking

The realization of the goal set out for developing tracking systems for EID to be able to forecast the outbreaks and the behaviours of the diseases according to the technology roadmap can only occur if all APEC economies adopt the roadmap and integrate it into their national policies. The policy should be championed by a government body that can coordinate with other economies in the implementation and evaluation.

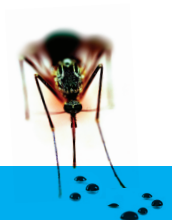
In the short term, APEC member economies should focus on public awareness regarding the EID technology roadmap with the emphasis on the short term policy emphasizing the integration of tracking technology through standardization and R&D programs. An establishment of an APEC-wide EID tracking center for information exchange and training will greatly help the managing the roadmap activities with great efficiency.

In the medium term, the general public should be made aware of the importance of the traceability infrastructure and the need to collect data that might be considered private. Implementation of cross-border pilot projects will demonstrate the benefits of tracking infrastructure and verify the interoperability of different tracking technologies.

In the long term, there should be a policy on continuous and systematic monitoring/ surveillance of vectors and other factors contributing to the emergence of infectious diseases so that breakouts and spreading of the diseases can be forecasted with high accuracy.

TABLE 20: POLICY RECOMMENDATIONS FOR TRACKING

Actions	*Short Term*	*Medium Term*	*Long Term*
Technology	• Standard development to promote integration of tracking technologies • R&D Programs on disease detection, device miniaturization, energy management, sensor technology and localization technology. • Exchange of experimental samples	• EID tracking pilot project for technology integration	• Build ICT infrastructure to support EID tracking in each APEC economy • Systematic surveillance of vectors based on research network • Continuous microbial monitoring system
HRD & Public Information	• International seminar on APEC EID roadmap	• Annual APEC forum for EID experts	• APEC EID experts coordinator training program
Regulation & Organization	• Set up an APEC-wide EID tracking center for information exchange and training • Full implementation of IHR2005 • Fast track immigration counter for APEC scientists • Invisible fence for EID suspect quarantine	• International agreement on cross-border issues for human/animal • Government provides incentives for legal immigrants to use tracking mobile phone in exchange for social welfare • Government support for collecting human physiological data	



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Chapter Ten: Vaccines

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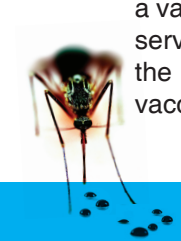
Introduction to Vaccines

A hundred years ago, infectious diseases were the main cause of death worldwide, even in the most developed countries. However the development of vaccines and the application of mass immunisation programs have proven successful in controlling or even eliminating diseases. Thus, before a vaccination program eliminated all natural occurrences of smallpox in 1977, the disease threatened 60% of the world's population and killed one out of four victims. Between 1999 and 2003, measles deaths dropped worldwide by almost 40% due to vaccination.[1]

Vaccination is one of the most cost-effective health-care investments available. Based on data in developed countries there is an order of magnitude multiplier in savings in health-care per dollar invested in a vaccine dose.[1] In developing countries the outcome is seen in greatly increased survival rates. However immunisation must be maintained to be effective. History shows that a decrease in coverage leads to the re-appearance of diseases in a previously protected population.[2]

In maintaining immunisation it is necessary to have continuous upgrading as drug resistant strains develop and potency decreases. Thus, in the case of the most common type of influenza virus, A (H3N2), vaccines are updated on an annual basis by the World Health Organization (WHO) because the virus evolves so quickly. A committee of scientists meets twice a year to select the strains for use in the vaccine for the next influenza season.

One of the serious challenges to creating influenza vaccines is that the global migration of viruses has been a mystery. Recent research on worldwide samples of the H3N2 virus has identified different strains and traced their movement patterns out of the East and South-East Asia circulation network to Europe and North America and then to South America.[3] Once viruses leave East and Southeast Asia they rarely return but, for a variety of reasons, they continue to circulate year – round in East and Southeast Asia, serving as a source for the rest of the world. Surveillance within E-SE Asia will enable the characteristics of viruses elsewhere to be forecast each year leading to improved vaccines.



In the case of avian influenza, vaccines have been produced based on whole, inactivated virus particles of H5N1 strains from outbreak regions. These have yet to be used for vaccination, but there is widespread concern that the viral strain that could cause a pandemic will be a mutated form, invalidating the stockpiles based on the current strain. However, since large scale vaccine production is not expected to commence until about three to six months following the emergence of a pandemic virus, the vaccine could be updated using existing facilities.

Should a pandemic occur, the available supplies will be used in developing countries as manufacturing capability for avian influenza virus is overwhelmingly concentrated in Europe and in North America. Current production capacity - estimated at around 300 million doses of trivalent seasonal vaccine per year - falls far below the demand that could arise during a pandemic.
It is not easy to increase capacity by setting up plants in developing countries, since vaccine manufacturing by standard methods is often more challenging than manufacture of therapeutic medicines and strict quality control is necessary. China is a notable exception for avian flu vaccine but India and Thailand have vaccine production for other diseases. A strong driver for increased research is that new approaches to vaccine development may allow more extensive production facilities in developing countries.

Roles of Vaccines in Combating EID

Based on the RAND Life Cycle Model for EID, vaccines are clearly in the forefront of an integrated approach to combating EID. Thus they can assist in prevention of disease outbreaks (Preventive Measures) and also in controlling outbreaks (Prevention of Spread). There are several phases in vaccine development and use. Firstly the disease has to be recognised and identified as a major threat. Secondly the vaccine has to be developed in the laboratory and then trialled for efficacy and possible adverse effects. Thirdly a vaccination program has to be established and maintenance assured. Further, a complementary drug needs to be developed to deal with situations where the immunisation program for various reasons is not effective or where an unexpected variant emerges.

The traditional methods for vaccine production use live or live attenuated viruses and then cultivate them in chicken eggs or cell culture, involving months of production time in dedicated facilities. Research and development is expensive as are time-consuming clinical trials involving people. As a consequence pharmaceutical companies have tended to concentrate on those vaccines which can offer the greatest return on investment in developed countries and the system is not very responsive to unexpected outbreaks of disease. Overall the global vaccine market forms only around 2% of the $US 240 billion pharmaceutical market. Strict regulatory regimes are operative in developed countries which inhibit vaccine development and which may not be applicable in developing countries. Thus the large pharmaceutical companies have protected their investments

by a network of worldwide patents which prevented competitors from entering the market. This disadvantages developing countries which cannot afford to buy vaccines to protect their populations.[4]

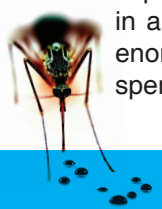
In order to meet the mounting threats posed by EID it has been recognised that there is a need for new approaches to vaccine development. The sequencing of the human genome as well as the genomes of other organisms such as pathogens, disease vectors, insects and animals has pointed the way to a new approach to vaccine development. The development of sophisticated analytical instrumentation has enabled rapid analysis of large numbers of genes and the proteins expressed by genes and these data have been analyzed using bioinformatics.

Many genetic sequences are discovered in advance of other, less easily obtained biological information and so-called 'reverse genetics' attempts to connect a given genetic sequence with specific effects on an organism .The phenotype is altered and the effect on the organism is studied. Thus it is possible to rapidly produce candidate vaccines by reverse genetics on live viruses by modifying the phenotype associated with high virulence.

Further, increased computing capability and software has enabled advances in molecular modeling for new types of vaccines e.g. synthetic carbohydrate antigens and genome-derived, epitope-driven vaccines.

A more mechanistic application of reverse genetics to vaccines has been termed 'reverse vaccinology'[5]. An example is the development of a vaccine against meningococcus type B,a bacterium which causes meningitis, a severe disease of the brain.[4,5] There are five known serotypes or groups of meningococcus known at present, termed A,B,C ,W and Y. The first three are responsible for most morbidity and mortality. Serotype A is responsible for most major epidemics in developing countries in Africa and some countries in Asia and South America but so far a vaccine has not been developed because it is a lower priority for developed countries which are affected by serotype C for which a vaccine has been developed in the UK. Serotype B also affects developed countries but until recently there has been no vaccine despite four decades of research. The problem is that some of the molecules that present target antigens on the bacterium are very similar to those in human tissue and the immune response produced by vaccination with such antigens can produce severe side-effects.

In a new approach the entire sequence of the genome was determined and the proteins likely to be surface components were identified using computer predictions on the basis of their structure. Some 600 candidate proteins were selected of which 350 were expressed by standard molecular biological techniques; of these, 29 were promising in animal trials. Five of the latter were included into a vaccine for clinical trials. This enormous program of work was completed in only 18 months compared to the 40 years spent unsuccessfully in standard approaches.



The desired immune response to vaccines is the production of antibodies and this can be enhanced by adding substances called adjuvants. Although these substances have been known for many years and have been used to elicit an early, high or long-lasting immune response with conventional vaccines, their action is still not well understood. Given that the newly developed synthetic vaccines are so far poor immunogens, adjuvants are required to provoke immune response. More research is needed on possible new adjuvants.

This approach of converging technologies of genomics and information technology enables a new paradigm for vaccine and drug development but it is clear that the structure of market incentives for vaccine development especially for emerging and neglected diseases that predominantly affect poorer countries needs reassessment if breakthroughs are to be made.[4]

Thus new approaches to the production of generic vaccines and drugs which are made available at low cost are taking place through the formation of national and international partnerships between Governments and pharmaceutical companies and between large private philanthropic groups and pharmaceutical companies such as the Medicines for Malaria Venture, the Global Alliance for TB Drug Development and the Global Alliance on Vaccines and Immunisation..

A critical step is that of immunisation.

It is now recognised that diseases result from the interacting effects of many genetic, environmental and social factors and a broader approach is needed in developing immunisation programs. Different genes may be associated with disease susceptibility in different human populations, as in the case of malaria. The implication is that results obtained from genome epidemiological studies in one part of the world, or one human population, may not be transferable to other populations.[6] A vaccine against a particular disease may be vital in one economy but marginal in another. Highly effective vaccines against diseases in developed counties may be of limited significance in developing countries. While there are a number of studies on disease susceptibility genes in developed countries there is a need for more studies in developing countries to prepare for EID through vaccination.

The mode of delivery of vaccine is important particularly in developing countries where sterilisation of medical instruments is often difficult. Attention is being directed to delivery either orally or by nasal spray. However it is necessary to ensure that local cultural issues regarding vaccination are adequately understood and taken into account. Effective delivery systems would be essential in dealing with a pandemic and new systems based on nanoparticles offer exciting possibilities.

Roadmap Discussion

The discussions at the workshops covered the topics highlighted above and identified possible alternative technologies for vaccine development, production and delivery resulting from convergence of disciplines. At the roadmapping workshop in Japan, the international group of drug/vaccine experts worked together to identify the key requirements for future drug and vaccine development.

The results from the group discussion can be summarized for three time periods as;

- For the short term (2007-2012), the development of drugs and vaccines should aim for improving efficacy and reducing side-effects,
- For the medium term (2013-2017), the development of drugs and vaccines should focus on improving drug and vaccine effectiveness and safety along with the aim for reducing production cost and complexity,
- For the long term (beyond 2017), the requirements for future drug and vaccine development should be aimed at improving stability and developing a long-lasting drug and vaccine which can be kept at room temperature.

On the basis of these clear medical requirements, the group of experts continued their work at the workshop in Chinese Taipei to determine technologies that can be used to support the development, production and delivery of new drug and vaccine. Major technical and political challenges hindering the development progress of those technologies were also identified along with the type of activities and R&D programs needed to overcome the challenges. The vaccine roadmap is shown in Table 21.

To achieve the short term goal by 2012, the experts identified that technologies supporting the development of new drug and vaccine will primarily rely on the basic characterization of the molecular structures using biological properties of pathogens with epitope mapping process. In addition to the basic characterization, the novel strategies supporting the development of polyvalent vaccine should also be explored. The vaccine efficacy can be improved by using cell-targeted techniques for drug delivery systems. The vaccine production can be made more cost-effective and easier for manufacturing by applying serum-free mammalian cell culture system, baculovirus/insect cell system, or yeast expression system. However, there are a number of challenges that could possibly hinder the development progress of such technologies. The major challenges are caused by cumbersomeness of conventional methods, imperfect algorithms, limited access to supercomputers supporting “molecular modeling”, absence of universal protocol for protein crystallization and constant mutation of pathogens, etc. To overcome these challenges, many activities and R&D programs need to be carried out, for example *in silico* modeling for the development of vaccine delivery system, human resource development in an area of bio-informatics, diffusion of comprehensive study on pathogenesis of the agents, establishment of virus inventory center, etc.

For the medium term (2012-2017), the experts recommended a focus on the uses of novel strategies such as proteomics, microarray and molecular modeling to improve drug/vaccine effectiveness and safety. The development of highly effective drugs/vaccines should be emphasized in this period by applying novel approaches using DNA and reverse genetics.

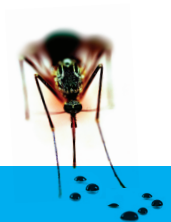
The production cost has to be reduced by using cell-free system for vaccine or therapeutic protein expression as well as genetically modified microbial factory system. The efficacy of drug delivery will continue to be improved by applying specific cell or tissue targeted systems. The major challenges in this period are caused by the lack of standardization of antigens and the difference in the nature of pathogens. To overcome these challenges, the expert community must work on creating chemical libraries to exchange their information, on setting up procedures to manage patent restrictions and on facilitating international coordination for human clinical trials. R&D investment is required in the area of nucleotide sequencing technology for real-time detection of pathogen mutation.

For the long term (beyond 2017), the experts targeted the need to improve drug/vaccine stability. To this end, DNA-based vaccine technology should be explored along with the new production technology to support the development of polyvalent vaccines. Also, technologies supporting nanomedicine are needed to improve drug delivery leading to greater drug efficacy.

Collaboration among laboratories across APEC member economies is required so that the key challenges caused by the lack of animal testing and safety data can be removed. The outputs from the workshops are brought together in the vaccine roadmap as shown in Table 21. This indicates the key areas where the convergence of technologies is the driver for progress. For example, modeling technology is necessary as it plays a major role in vaccine development by anticipating side effects, by screening vaccines with novel delivery needs, by testing personalized drug/vaccine design etc. The main challenges in achieving the targets are the creation of a suitably skilled workforce, improved availability of high quality infrastructure, removal of restrictions imposed by the present patent system, the creation of networks for sharing of information and capabilities, as well as adequate financial support to undertake prevention-mitigation-preparation-training.

Table 21: Technology Roadmap for Vaccines

		2007 - 2011	2012 - 2017	Beyond 2017
Medical Req't		• Improve efficacy • Reduce side effect	• Improve effectiveness & safety • Reduce production cost	Improve stability
Technology	Development	**Basic characterization** E.g., Biological properties of pathogens; Epitope mapping	**Highly competent vaccine/drug** Using novel approaches (DNA vaccine and reverse genetics)	DNA-based vaccine technology plus other components such as cytokines and adjuvant
		Novel strategies E.g. Polyvalent vaccine development	Proteomics, microarray, molecular modeling for designing immunogens	
	Production	**Cheaper and easier manufacturing** Serum-free mammalian cell culture system, baculovirus/insect cell system, or yeast expression system	Cell-free system for vaccine or therapeutic protein expression Genetically modified microbial factory system	Polyvalent Vaccine Production (Universal Vaccine) Application of reverse genetics
	Delivery	**Improvemt of drug delivery efficacy** Drug delivery system: Cell-targeted Pharmacokinetics and phamaco-dynamics	Targeted drug delivery system: specific cell or tissue targeted	Nanomedicine for drug delivery system
Challenges Technical & Political		• Cumbersome conventional methods. • "Molecular modeling" Imperfect algorithms, Limited access to supercomputers • Absence of universal protocol for protein crystallization • Constant mutation of pathogens Few approved cell lines for vaccine production	• Standardization of antigens • Different immune responses to the same vaccine and low amount of antigens Difference in nature of pathogens "Recombinant Protein" and its true form	• Poor results in human subjects • Lack of data on safety issues • Lack of data on animal testing
		Patent and budget restriction		



Activities and R&D Programs			
	• *In silico* modeling for development of vaccine delivery system • Generating Human resources for bio-informatics • Comprehensive study on pathogenesis of the agents • Virus inventory center	• Development of diagnostic kits and rapid determination of the antigen content • EID surveillance for development and production of vaccines	• Collaboration between laboratories in material, data and information sharing • Improvement of Safety + mmuno-genicity of vaccines
	• Chemical libraries exchange information • Support for patenting procedures • International coordination of human clinical trials	• Powerful nucleotide sequencing technology for realtime detection of pathogen mutation • Improvement of bioinformatics	
	• Urgent need to validate vaccines • Detection and removal of contaminating material	Risk assessment of the GM organisms and cell lines used for vaccine production Set-up a core laboratory with state-of-the-art technologies	Multi-disciplinary research with collaborative efforts

Policy Recommendations for Vaccines

1. Vaccine development, production and delivery are essential components of a global strategy to combat EID. National strategies for health systems and for science and technology in all countries must recognise this in their planning for infrastructure and for skilled people.
2. Vaccine development is currently expensive and controlled by a few companies in developed countries .It is essential that R&D on new approaches using converging technologies is strongly supported by governments of developed countries. This can be done through public-private partnerships to ensure equity of access to the whole population and thence to developing countries.
3. R&D should be directed towards more rapid development based on genome manipulation and molecular design and simpler production techniques. This may enable more technology transfer to developing countries for domestic production. However the difficulties of such transfer are considerable in terms of lack of skilled manpower and quality control.
4. Vaccines produced in developed countries may not be suitable for application in developing countries where EID are most prevalent. Large-scale population studies are essential for understanding the details of genomic influence on human health and diseases. Similarly global studies are needed to track transmission paths and to understand mutation patterns of EID.
5. The effective delivery of vaccines by mass vaccination techniques is critical to successful control of EID. This raises the issue of “business” versus “public health” models for vaccination. In 2008 about 2.5 billion people earn less than US$2.5 per day and thus cannot afford vaccination. Existing global health systems need to be

strengthened and expanded to overcome this situation.

6. Converging technologies clearly have much to offer in the development and delivery of vaccines but need to be seen as part of an overall strategy for combating EID. Since the problems are global ones crossing national boundaries, appropriate international communication and co-operation is necessary to ensure optimum use of infrastructure and skilled people.

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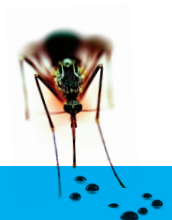

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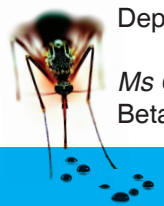

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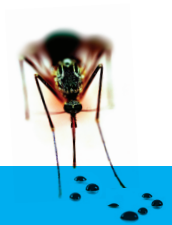

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