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**Bioterrorism Preparedness for Infectious Disease**

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**Bioterrorism Preparedness for Infectious Disease (BTPID)** as part of homeland defense initiatives is advancing rapidly, with the Center for Disease Control (CDC) taking the lead in mandating improved surveillance and management for States to follow, centered around 6 major focus areas with 17 critical capacities. Significant opportunities exist for new research and development of bioinformatics and telecommunications solutions for BTPID that would complement CDC led initiatives. The objectives of this planning grant are to:

1. Identify problems and propose bioinformatics and telecommunications solutions for BTPID surveillance for both military and civilian populations emphasizing the use of secure, redundant, real-time networks,
2. Identify problems and propose bioinformatics and telecommunications solutions for BTPID outbreak management.

A multidisciplinary team is conducting the study consisting of members from the Department of Defense, State of Hawaii Department of Health, Maui High Performance Computing Center (MHPCC), University of Hawaii (Telemedicine, Environmental Health, Bioinformatics, Infectious Disease), University of Southern California (Image Processing and Informatics Lab) and Stanford University-NASA Ames (National Biocomputation Center). Information has been gathered through meetings, retreats and literature reviews regarding problems and solutions for a variety of potential scenarios such as Anthrax, Dengue, Smallpox and SARS epidemics. In addition to working meetings, a summit was hosted to gather experts in the field for technology demonstrations and information gathering for subsequent analysis for BTPID solutions. The information acquired is currently archived and available through a website and has been incorporated and referenced together with new information for the analyses and recommendations portion (year 2) of this project. In separate modifications to the original cooperative agreement, a report is being prepared for DTRA and their review to assist in chemical and biological preparedness, and funding was initiated for a clinical research center in Thailand. Lastly, a travel modification was provided to support the Asia-Pacific Military Medical Conference in Hanoi, Vietnam in May 2005.
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INTRODUCTION

Bioterrorism preparedness for infectious disease (BTPID), as part of homeland defense initiatives is advancing rapidly, with the Center for Disease Control (CDC) taking the lead in mandating improved surveillance and management for States to follow, centered around 6 major focus areas with 17 critical capacities. Significant opportunities exist for new research and development of bioinformatics and telecommunications solutions for BTPID that would complement CDC led initiatives. With this in mind, the funded effort, which is a planning study, intends to identify problems and potential solutions related to bioterrorism (BT) preparedness. The first year of this work was focused on data gathering. The second year focused on analysis and potential solutions (supplemented by additional literature reviews and meetings as required) to yield recommendations that could be utilized as part of a homeland defense initiative and be applicable as part of a force protection initiative for garrisoned or deployed DOD units, who are highly visible targets for terrorist or conventional biological warfare threats. A multidisciplinary team is conducting this study and consists of members from the Department of Defense, State of Hawaii Department of Health, Maui High Performance Computing Center (MHPCC), University of Hawaii (Telemedicine, Environmental Health, Bioinformatics, Infectious Disease), University of Southern California (Image Processing and Informatics Lab) and Stanford University-NASA Ames (National Biocomputation Center).
The following is a description of the research accomplishments associated with each task in the Statement of Work. The statement of work is as follows:

The main objective of this effort is to identify problems and propose alternative bioinformatics and telecommunications solutions for (a) BTPID surveillance for both military and civilian populations emphasizing the use of secure, redundant, real-time networks and (b) BTPID outbreak management. This will be accomplished in two steps: Year 1 focused on data gathering (refer to previously submitted annual report), year 2 focused on demonstration, analysis, and recommendations.

Year 2 work was accomplished through:

*Definition of Bioterrorism problem areas, identification of needs, description of solutions and recommendations for future research.*

The past grant year was challenging, yet successful on many fronts, including three modifications to the current Bioterrorism Preparedness grant:

- The Dengue outbreak in Hawaii and its synopsis is provided as part of this annual report. It provides an interesting look at an infectious disease outbreak that occurred synchronously with 9/11, thereby causing difficulty in managing the outbreak due to disruption of airline flights and processing of specimens from a national laboratory in CONUS US. As such, this report provides valuable insight for the development of local and regional initiatives in preparation for bioterrorism acts. Dengue can also serves as a model for vector borne illnesses. (*See Appendix A*)
- A meeting was conducted in June 2004 exploring the possibility of developing a Joint Clinical Research Center (JCRC) in Infectious Disease in Thailand. This provided an important look at the possibility of establishing such a Center, where clinical research can be readily conducted on patient populations with infectious
diseases, that all are listed as potential bioterrorism agents by the CDC. (See Appendix B)

- **Modification #1**: Based on the June meeting in Bangkok, the grant was modified with additional funding to assist with the development of a Joint Clinical Research Center in association with the Armed Forces Research Institute of Medical Sciences (AFRIMS), Phramgkutlao Medical Center (PMK) of the Royal Thai Army, and the University of Hawaii (UH). Initial results are positive, with UH grants in HIV being the first to run through the Center. The grant either provides for infrastructure or for pilot projects. Currently, no funds have been deployed for projects, but this is entirely possible as budgeted and will require IRB approval. However, plans are being developed now to fund basic infrastructure such as equipment and personnel to provide the administrative support to successfully obtain grant funding.

- **Modification #2**: An education and training modification to the current grant was also provided to assist with the further development of the JCRC. Providing education and training activities is a natural extension of TATRC and this initiative, providing important inroads into relationships being developed with potential infectious disease research partners in Southeast Asia. The major initiative being supported through this modification is the Asia Pacific Military Medical Conference (APMMC) that is primarily funded through US Army Pacific. In conjunction with the Winter Institute for Simulation, Education, and Research (WISER), the University of Hawaii will provide training to military medical officers at this annual meeting in May 2005 in Hanoi. The summary of this training will be provided in next year’s annual review. Discussions have been ongoing with the Course Directors and WISER to develop the curriculum for the meeting.

- **Modification #3**: The final positive development was modification of the grant to provide support to the Defense Threat Reduction Agency (DTRA). Through the individual hired for this program, UH provided valuable short-term support to DTRA in providing a report to assist DTRA in defining goals, developing interagency agreements, and progressing rapidly in preparation against chemical and biological warfare. This report is still under preparation and will be presented in next year’s annual report.
KEY RESEARCH ACCOMPLISHMENTS

Dengue Fever Outbreak Hawaii, 2001
A Bioterrorism Model for Vector Borne Illnesses (See Appendix A).

Meeting on Establishing a Joint Clinical Research Center (JCRC), Thailand

The agenda and summary of key presentations including US government (AFRIMS), Thai government (PMK Medical Center, Royal Thai Army), international Clinical Research Organizations (PPD), and University of Hawaii are summarized (see reportable outcomes section). The conclusion of the meeting was that the University of Hawaii through a collaborative effort could realistically support a JCRC in affiliation with several partners. This validated the funding request to TATRC that was funded later in September 2004.

Modification #1: Support of a Joint Clinical Research Center (JCRC), Thailand

Based on the fact-finding meeting held in June, the grant was modified to provide infrastructure building and funds for pilot projects for the JCRC. Currently, meetings with the partners have been progressing but no hires are planned for 2004. At the start of 2005, in collaboration with an HIV grant funding through UH, a nurse will be hired through the JCRC to assist with generalized center administration, while her clinical role will be funded through the HIV grant. This administrative support for the Center in general will facilitate additional grant submissions, as grant writers can concentrate on writing grant as opposed to dealing with day-to-day Center administration. In addition, non-HIV related grant applications will be submitted through a US PI, who is affiliated with both AFRIMS and Mahidol University in Thailand. He is an internationally respected researcher who will be hired off the HIV grant for his clinical work, but will also be hired off of this JCRC grant for research development. As such, he will not be restricted from developing non-HIV related grants that will be conducted with other research groups at UH. Some funds through the BT grant will be used to support grant preparation and related travel.

Modification #2: Education and Training in Southeast Asia, Facilitating JCRC Activities
This modification assists the University of Hawaii (UH) to enhance its presence in SEA, which will help to foster its bioterrorism related infectious disease research in Thailand and SEA in general. UH has a growing relationship with the Asia Pacific Military Medical Conference (APMMC), with Dr. Burgess (UH-PI) being a frequent attendee and speaker in the past while in the military, and more recently after retirement. The conference assembles all SEA military medical officers for each week annually.

Dr. Burgess has been in close collaboration with COLs Benjamin Berg and Dale Vincent who are the Course Directors for APMMC, and they feel strongly that advanced training with mannequins would be an outstanding method to bring advanced simulation based training to APMMC, while also providing a more significant presence for the University of Hawaii in SEA. Initial meetings in Vietnam were conducted in July with Dr. Burgess and the host Vietnamese military medical officers (trip funded through another source), and they concur with the UH providing for two days didactic sessions, followed by a day-long training session for Vietnamese medical officers.

This training is possible through UH’s working association with the WISER institute of the University of Pittsburgh Medical Center, who have developed an extensive on-line as well live training curriculum that are used together for training. UH and WISER will partner in delivering the program at APMMC. Through this process, simulation training could become an annual event at APMMC, and UH will develop stronger associations throughout SEA, thus making it more capable of expanding its infectious disease research interests in the region.

In the last quarter of CY 04, meetings were conducted with WISER, UH, Course Directors, and Laerdal surrounding the meeting. Laerdal will provide 3 mannequins and a guest speaker, which will assist immensely with training. The results of this training session will be reported on in the next annual report.

Modification #3: Report to Defense Threat Reduction Agency on Chemical and Biological Preparedness Activities
Preparedness against Biological warfare and terrorism agents is of central interest to this cooperative agreement, and concern revolving Chemical agents is an important, related area that provides further depth and value to the granting agency. Operationalizing these Chem-Bio (CB) capabilities is an important task, as old products are revitalized, and new products are introduced to meet the threat.

A strong understanding of the science and technology of these products, as well as the deployment issues surrounding both industry and government are critical issues for the nation in this new era of terrorism. Products and platforms are taken from prototype to deployment, involving issues of technology transfer and coordination with multiple US government agencies in the CB preparedness space. The Technology Transition Division of the Chemical and Biological Defense Directorate of the Defense Threat Reduction Agency has specific needs to meet to thwart the CB threat. Specifically, they must perform the following: develop program objectives, and direct all planning, coordination and integration, execution, and evaluation activities associated with these objectives; direct and facilitate the activities of senior civilian and military operators, engineers and scientists planning and executing field operations; interact with senior managers in OSD and other departments and representatives of foreign governments; coordinate with all organizations and stakeholders involved in the USPACOM Biological Warfare Countermeasures Program and the USAF Counter CBRNE Program, including the Deputy Assistant to the Secretary of Defense (Chemical and Biological Defense), JS J8 JRO CBRND, CIA, DIA, USPACOM staff/components/subunified commands, HQ USAF/XO staff, Joint Program Executive Office (Chemical and Biological Defense), Joint Requirements Office for CBRN Defense, USAF Institute for Operational Health, US Army Medical Research Institute for Infectious Diseases, Edgewood Chemical Biological Center, Armed Forces Research Institute for Medical Sciences, USAF Counterproliferation Center, the military Services and Service doctrine and training centers, the national laboratories, industry and academia.

The University of Hawaii through its Bioterrorism Preparedness cooperative agreement provided a subject matter expert to assist DTRA in the time of transition, and this was completed on 31 December 2004. Through this short-term involvement with DTRA, a non-classified report will be generated with important lessons learned regarding the issues of research and development.
technology transfer, and interagency cooperation. This report will serve as a valuable roadmap for DTRA and others developing solutions for the federal government. As the period of service ended 31 December 2004, the report is still under preparation and review by DTRA. It will be presented in next year's annual report.
REPORTABLE OUTCOMES


See report in Appendix A.

2. The agenda and summary of key presentations including US government (AFRIMS), Thai government (PMK Medical Center, Royal Thai Army), International Clinical Research Organizations (PPD), and University of Hawaii are summarized in Appendix B.

Appendix A-1 contains the agenda of the event. The Bioterrorism Preparedness summit took place from 15 June 2004 until 18 June 2004 in Bangkok, Thailand. Appendices A-2 to A-5 contain presentations shown at the conference. A-6 donates the Strategic Plan. Biographical sketches of various people involved are available in Appendix A-7 and A-8.
CONCLUSIONS

The second year of this effort was successfully completed and provides a valuable foundation of knowledge, access to expertise and potential solutions. A bioterrorism event resulting in mass casualties will occur in the future. Terrorists are acquiring the means and knowledge to inflict serious harm to populations and, with time, can become sophisticated in their methods. A window of time exists to identify various solutions and establish the necessary expertise links to ensure focused research and technology utilization to help prevent and defend against acts of bioterrorism.
REFERENCES

Publications


Presentations


Introduction

The story of Hawaii’s 2001 Dengue Fever outbreak is an important one -- the situations, deficiencies and solutions experienced by Hawaii during this time can be applied to our thinking regarding the nation-wide push for effective bioterrorism preparedness (bioterrorism can be defined as the intentional use of microorganisms or toxins derived from living organisms to produce death or disease in humans, animals, or plants (1)). In many ways, the 2001 episode in Hawaii can serve as an interesting bioterrorism model for a complex 3-way terrorism event with the major spoke being of biological origin. Even though the main terrorist in this case was Mother Nature, the atmosphere of terrorism was strongly present due to the Dengue Fever outbreak occurring synchronously with the September 11th tragedy.

It is important to note that prior to the September 11th crisis, terrorism activities were of a different nature. Generally, terrorists planned and executed their events to make a vivid impact and gain attention with forceful or violent means, to protest policies or communicate their beliefs. Post 9/11 the terrorist goals are now to kill as many people as possible and also bring down a nation economically (we can call this “modern” terrorism) (2). They will obtain the necessary education to do it (such as learning to fly a commercial aircraft and possibly even to obtain college degrees and expertise in microbiology and techniques necessary for a thoughtful and sophisticated biological attack on a nation). We know now that they will take the necessary time to obtain this knowledge and eventually execute their goals as planned. We also learned that multiple attacks performed simultaneously are a distinct possibility and a successful strategy that can dilute the emergency relief response, manpower, and supplies, which in turn can result in a greater number of casualties, prolonged suffering and panic, and a prolonged recovery.

A major lesson from September 11 was that the unthinkable can happen -- terrorists educating themselves (through pilot school) to achieve 7 simultaneous disasters (4 crashed airplanes, 2 collapsed buildings in New York, and substantial damage to the Pentagon). The question regarding bioterrorism now is: are terrorists learning biological sciences in capable schools, possibly with access to infectious disease material that they can, with proper technique, replicate and spread using various dissemination modes. Much of the literature on bioterrorism caution that it is not a matter of “if” it will happen, but “when” it will happen. We currently have a window of time to prepare and Nature, with her periodic infectious disease outbreaks, has provided important experiences for us to find out our deficiencies in dealing with major biological events and find solutions.

The Dengue Fever outbreak in Hawaii was a valuable and unique experience in that it was actually a multiple crisis – perhaps similar to what might be encountered in
the future given the “modern” terrorist thinking discussed above (affecting masses of people, affecting the economy, several crises all happening simultaneously). Although the Dengue outbreak actually started in May of 2001 (the Hawaii State Department of Health (DoH) found this out retrospectively) the realization of an outbreak occurring happened on September 12th 2001. During this time the Nation was in crisis from the multiple World Trade Center/Pentagon attack. Also at this time the Anthrax-laced letters were appearing and infecting people (a crisis Hawaii post offices had to deal with also) (3). Thus, there existed a three-pronged emergency, complete with the grounding of aircraft resulting in a complicated and isolated situation for Hawaii.

The 2001 Dengue Fever outbreak in Hawaii is a good example of how outbreaks can occur (in this case brought by non-terroristic foreign travelers) and progress in a subtle manner before being detected and dealt with. The Dengue model is valid for bioterrorism preparedness, as the National Institutes of Health has upgraded Dengue Fever as a potential bioterrorism threat. This paper will discuss the nature of Dengue Fever, its history and emergence in Hawaii, and the 2001 Hawaii Dengue Fever outbreak experience – including the unexpected difficulties and findings, disadvantages/deficiencies, short-term and long-term solutions. We will then list strengths and capabilities necessary for dealing with a vector-borne biological event and relate the overall Hawaii experience to the National state of preparedness.

The Nature of Dengue Fever

Dengue fever (DF) is a flu-like illness characterized by symptoms such as high fever, severe headache, pain behind the eyes, muscle and joint pains, and rash. The virus is transmitted via the bite of various day-feeding mosquitoes. With Dengue Fever, there is a mosquito-human transmission with humans serving as reservoirs for the disease. There is no human-human spread of disease. Here, the “enemy” is the mosquito and defenses against the mosquito are key in protecting human health. Eradication of the mosquito is key to stopping the outbreak. There is currently no vaccine. Dengue fever has increased in both incidence and distribution over the past 40 years. Annually it is estimated that there are 20 million cases of Dengue infection worldwide, resulting in 24,000 deaths (4).

In 1944, Albert Sabin successfully isolated the virus that causes Dengue Fever and found that it belongs to the Flaviviridae virus family. There are more than 70 known members of the Flaviviridae family. Some examples include Yellow Fever and Japanese Encephalitis Virus (5). Flaviviridae are viruses that utilize humans, lower primates, and mosquitoes as hosts. The Dengue virus mainly relies on the mosquito Aedes aegypti as a vector to transmit it to human and primate hosts. Because dengue is an arthropod-borne virus, it is also classified as an arbovirus. The A. aegypti mosquito is an urban mosquito that thrives in pools of standing water. Peak transmission is associated with increased amounts of rainfall and mosquito density. Therefore, tropical climates are ideal for the mosquito to survive. Pools, puddles,
buckets of water, gutters, and people spending significant amounts of time outdoors aid in successful transmission of the virus.

Presently, there are four known serotypes of dengue virus. These are labeled DEN-1, DEN-2, DEN-3, and DEN-4. The different serotypes have the same morphology and genome; however, each serotype displays different antigens. Historically, DEN-2 is the prevalent serotype found in Southeast Asia and may be responsible to immunity against Yellow Fever. DEN-3 has been found in the Caribbean and DEN-1 has been found in the Pacific Islands (Hawaii, Marshall Islands). Exposure to any one of the dengue virus strains confers immunity to reinfection by the same strain. However, if a person once infected becomes re-infected with a different strain, there is an increased likelihood that the virus will be expressed as a much more severe form of the disease, dengue hemorrhagic fever (DHF), which has been compared to ebola in its symptoms, or dengue shock syndrome (DSS), characterized by extremely low blood pressure. Both conditions can be fatal and require immediate medical attention (5, 6).

**History of Dengue Fever**

The first recorded cases of Dengue Fever occurred in 1779 in Batavia, Indonesia, and Cairo, Egypt. In 1780 a Dengue epidemic was reported in Philadelphia, Pennsylvania. For the past 200 years, pandemics have been recorded in tropical and subtropical climates at 10 to 30 year intervals. The intervals of several decades between outbreaks occurred because the virus was not as rapidly transported as it is today. After WWII, with increased travel and consequent spread of Dengue viruses throughout the Pacific region and the Americas, the distribution of Dengue Fever has changed. The first epidemic of DHF occurred in 1953 in Manila, and the disease remained endemic in Southeast Asia for 20 years until it spread westward into the Indian subcontinent and China in the 1980’s and 90’s. DHF and DSS are now leading causes of hospital admissions and death in Asian children (5,6).

**Dengue in Hawai‘i**

The first recorded case of dengue in Hawai‘i occurred in 1893, when it was known locally as "boohoo fever," a name arising from the emotional distress that usually accompanies the disease. The first widespread epidemic of dengue appeared in 1903, when approximately 30,000 people were infected. Another epidemic lasted from 1912 to 1915. Not until 1943 did the virus reappear in an outbreak that infected about 1,500 people -- and killed three -- before it ran its course in 1945. The outbreak even prompted the closure of Waikiki. Experts suggest that the infection may have been transmitted from Fiji, which was experiencing an epidemic at the time. It was believed the virus was brought to Hawaii through U.S. servicemen who had traveled through the South Pacific. The epidemic in the 1940s led to an effort, supported by federal funds, to eradicate the vector, Aedes aegypti. This mosquito was eliminated from most areas, although it still remains in parts of Moloka‘i and the coast of West Hawai‘i from Kawaihae to Captain Cook.
However, where Aedes aegypti was eradicated, Aedes albopictus quickly took its place (7).

Since the last major outbreak, some cases of dengue have been reported in the state -- including 18 from 1992-2000 -- but all were among travelers who contracted the disease elsewhere. With an incubation period of from three to 14 days after initial exposure to the virus through a mosquito bite, an infected person can easily transport the virus unaware that he or she is a carrier. From about one day before the first symptoms occur (fever, severe headache behind the eyes, and debilitating joint pain) and for the next week, the infected person can pass the virus to a mosquito host. The mosquito passes the virus on to anyone it bites for the rest of its life, usually no more than three weeks.(7, 8).

The Hawaii 2001 Dengue Outbreak

Hawaii is considered the last domino in a Dengue Fever epidemic that swept across the Pacific in 2001. Thousands of people were already affected by the virus in Palau, Samoa, French Polynesia, New Caledonia, the Cook Islands, and the Philippines months before (9-14). The virus appears to have arrived independently on Hawaii’s various islands from Tahiti and American Samoa. It was the first indigenous outbreak of dengue fever in Hawaii since World War II (134). Experts believe that a major reason for the global emergence of dengue fever is increased air travel between population centers in the tropics, allowing for the exchange of the virus and other pathogens.

Hawaii had a Type 1 Dengue outbreak. Although most confirmed cases were in the Hana, Maui area, the virus had "seeded" across the island, with a small number of infections in many places. Other cases were found on Oahu, and also Kauai to a lesser extent. Investigation of these sentinel cases on each island demonstrated that they were probably due to other travelers returning from the South Pacific, as opposed to people transporting the disease from Maui. Only 10% of the cases reported themselves to physicians. This population had a tendency to self-treat, lived alternative lifestyles, lived in very remote and isolated sites. For this reason Dengue was in the area much earlier than September before the first case presented to a physician (retrospective analysis). Once the Department of Health team was onsite to deal with the outbreak, they went door to door (Dengue was spreading from house to house). Experienced health personnel who have seen Dengue before in other countries (Brazil) and worked to contain outbreaks elsewhere were involved in Hawaii’s outbreak. This was very fortuitous since these experts recognized Dengue early and convince the population that mosquito eradication measures must be taken. During their investigations, they observed that the vector in this outbreak was not the usual Aedes aegypti, but a less efficient one, Aedes albopictis. This was an unexpected finding which puzzled investigators initially (15). The mosquito concentration in Hana at that time was thought to be particularly dense by health department field agents.
When the first suspected case of Dengue reported to the Maui district Health Office (September 12, 2001), it was during the nationwide anthrax scare. Like other states, Hawaii had to respond to reports of suspected anthrax discoveries in the weeks following the September 11 attacks. Also during this time, the Centers for Disease Control and Prevention (CDC) was preoccupied with the anthrax scare and was not able to ship laboratory supplies to Hawaii so dengue cases and infected mosquitoes could be quickly diagnosed. Instead, blood samples and mosquitoes had to be shipped to a CDC laboratory in San Juan, Puerto Rico, resulting in a turnaround time of weeks (16). The situation was unexpected. Hawaii received inadequate assistance for the Dengue outbreak because too much was happening simultaneously elsewhere. Therefore, the lesson learned here is that if a biological event occurs in multiple regions of the US, the local and State levels should be prepared to respond.

During the Dengue outbreak, the Hawaii DoH had trouble storing samples to be sent to the CDC Dengue Fever laboratory in Puerto Rico. Due to the airplane grounding delay from September 11, Hawaii did not have a true Dengue diagnosis until 3 weeks later. At this point it was clear that Hawaii DoH should have its own analysis facility. In the meantime, as a quick alternative, some field diagnostic test kits were ordered (which also had to be shipped). By September 19 the diagnostic kits arrived and all of the initial blood samples tested positive. On September 21, CDC confirmed the field tests. During the 3 weeks of waiting for laboratory results, spraying of insecticide around homes was done. Spraying was initiated within one week of when the first patient arrived to a physician. Therefore the Hawaii DoH was able to implement its major strategy within the week to deal with eradicating Dengue, which included public education (through TV and community meetings) and mosquito habitat reduction (17, 18). Table 1 provides a chronology of events spanning one month after the first patient was examined.

Table 1. Chronology of Initial Events of the 2001 Hawaii Dengue Outbreak (8, 18)

<table>
<thead>
<tr>
<th>Date</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sept. 8</td>
<td>A state surveillance program began a few days before the first suspected Dengue Fever case.</td>
</tr>
<tr>
<td>Sept. 12</td>
<td>First suspected case of Dengue Fever reported to Maui District Health Office (DHO). 47 y/o female from Lower Nahiku (Hana), with fever, headache, myalgia, arthralgia, rash on palms/soles/legs, no recent travel history, WBC = 1,300; platelet = 50,000; husband and son with similar illness, other community members with “Tahitian Fever.”</td>
</tr>
<tr>
<td>Sept. 13</td>
<td>Maui DHO investigates family of case in lower Nahiku</td>
</tr>
<tr>
<td>Sept. 14</td>
<td>Febrile illness alert issue statewide by DoH</td>
</tr>
<tr>
<td>Sept. 17</td>
<td>DoH investigators from Oahu arrive on Maui to assist</td>
</tr>
<tr>
<td>Sept. 19</td>
<td>Maui Health Lab reports anti-dengue IgM+ results</td>
</tr>
<tr>
<td>Sept. 20</td>
<td>Vector Control begins mosquito fogging in Nahiku. Sites were sprayed on Maui, Oahu, Kauai, and the Big Island</td>
</tr>
<tr>
<td>Sept. 21</td>
<td>CDC lab confirms Dengue infection in initial cases</td>
</tr>
<tr>
<td>Sept. 23</td>
<td>Health Advisory to Maui health care providers</td>
</tr>
</tbody>
</table>
### Table

<table>
<thead>
<tr>
<th>Date</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sept. 24</td>
<td>Active surveillance initiated on Maui (14 sites)</td>
</tr>
<tr>
<td>Sept. 28</td>
<td>Health Advisory to ER and hospital staff statewide</td>
</tr>
<tr>
<td>Sept. 30</td>
<td>CDC officials arrive to assist in investigation</td>
</tr>
<tr>
<td>Oct. 1</td>
<td>CDC isolates DEN-1 virus from sera of initial cases</td>
</tr>
<tr>
<td>Oct. 2</td>
<td>Active surveillance expanded to 28 sites statewide</td>
</tr>
<tr>
<td>Oct. 8</td>
<td>First non-Hana and Kauai cases confirmed</td>
</tr>
<tr>
<td>Oct. 9</td>
<td>Active surveillance expanded to 51 sites statewide</td>
</tr>
<tr>
<td>Oct. 12</td>
<td>First Oahu case confirmed</td>
</tr>
</tbody>
</table>

**Communications/Media**

During the outbreak, communication action taken by the Hawaii Department of Health (19-20) and the Maui County Civil Defense Agency (21) included information/brochures, press releases, travel advisories, advisories to Health Care Providers, contact numbers on their websites. Local newspapers provided information as to the progression/eradication of the disease in Hawaii (22-26), progression of Dengue in other Pacific nations (9-14) and perspectives from health officials (25, 27-30). Town meetings and a dengue phone line (initially receiving 1000 calls a day) were a key component to educate and inform the public (31).

The state and counties launched a massive public education, outreach and cleanup program to emphasize the importance of eliminating mosquito-breeding areas to prevent the spread of the virus. Television and radio public service announcements were launched to encourage residents to clean from their neighborhoods any debris or containers holding water. State officials worked with the visitor industry to inform all arrivals of the outbreak. About 1,000 tourists per day were receiving informational brochures and mosquito repellent from a tourist information site set up on the road to Hana. Three other roads into the area were closed because of high risk (18). The Department of Health decided to inform the public on the threat and response taken knowing that the immediate effects on tourism might be negative but the long-term consequences would improve (31).

**Technology Utilization**

The use of technology was important in characterizing the outbreak, identifying hot spots, and communicating data and instructions. Health officials from the Centers for Disease Control and Prevention, the Hawaii State Department of Health, and the Maui County Health Department teamed with the Pacific Disaster Center (PDC) to perform a joint analysis of the outbreak. The PDC was asked to use its Geographical Information System (GIS) and Global Positioning System (GPS) technology and capabilities to perform data collection, mapping, and analysis in support of a wide range of activities throughout the planning, operational, and analytical phases of the assessment process. Techniques used were Dengue Diffusion Patterns and Disease Vector Modeling (spatial model schema). PDC created maps for investigators in the field utilizing remote sensing (vector control mapping) (4, 32). An important lesson learned was that GPS mapping was useful...
when used on a small town/village level to delineate “hot spots” but became less useful on an island wide level where normal maps would suffice (31).

Health officials working onsite in Maui later expressed that telemedicine would have helped in consulting with other experts (information exchange would enhance better decision-making). Contacting experts in real-time, receiving news in real-time via telemedicine technology would have helped. The telephone was very useful and was utilized for verbal communications to find out regions where the Dengue Fever was and regions where it was not. This helped to rapidly map the Dengue affected areas (31).

Factors that Helped/Hindered Progress

There were several factors that delayed detection and action against the Dengue outbreak. These include (33):

- The remoteness of the setting (mainly concentrated in the Hana Maui area) that made communications difficult, with sporadic cell-phone coverage.
- The tendency for the affected population to self-treat illness. These people believed they had the “Tahitian flu” and chose to treat it with their own herbal remedies. Only 10% of cases reported to a healthcare facility.
- Confirmatory diagnosis was delayed due to planes being grounded post 9/11, with no rapid diagnostic tests available in Hawaii.
- The community was reluctant to respond (to seek medical attention, allow the use of pesticides near their homes) until confirmatory tests had been done.
- Uncertainty regarding the progression the disease would take since the vector of this Dengue outbreak was not the usual one (Aedes albopictus) and considered an inefficient vector for Dengue.
- Although the military presence in Hawaii is an advantageous resource during a crisis or disaster, many military resources were not able to assist during the outbreak since all were standing by for homeland defense initiatives or deployment to Afghanistan.

Several advantages helped to balance the delays and prevented the outbreak from becoming worse:

- Aedes albopictis is an inefficient vector for Dengue Fever. The situation was different during the World War II outbreak when Aedes aegypti infected thousands of people in Hawaii.
- Experienced personnel who have worked extensively with Dengue before were on staff at the Health Department. Their quick recognition of symptoms provided an early awareness.
- Technological help (modeling, mapping) was local and readily available (Pacific Disaster Center)
After the Outbreak

The last reported case of Dengue in Hawaii was the week of February 3, 2002. In total, there were 119 confirmed dengue cases in the state from 27 May 2001 to 3 February 2002. The peak number of cases occurred in September-October 2001 (34). Although the outbreak has been under control for quite some time, the State Department of Health cautions that Hawaii will always be at risk for Dengue and must continue to control mosquito populations. The disease normally recurs during the warm summer months and anyone infected with the virus can easily bring it back to Hawaii from endemic areas in the world. It also can be easily established in Hawaii if residents fail to take precautions, including the continuing effort to control mosquito populations around their homes (35).

The Dengue outbreak experience has resulted in a number of improvements in the health system. For example, on May 10, 2002, the Hawaii State Department of Health unveiled plans for its long-term dengue fever management strategy. The plan included a long-term dengue surveillance system statewide, a statewide mosquito population survey, and ongoing vector control efforts (36). The statewide surveillance system includes ongoing sampling of patients who demonstrate dengue like symptoms. This provides the Health Department with valuable data, giving officials an opportunity to catch an outbreak before it spreads. In addition to monitoring the situation in Hawaii, the department will be keeping up to date with outbreaks around the world.

The statewide mosquito population survey was initiated in March 2002, and helps to clearly identify problem areas and the various species of mosquitoes found in Hawaii. Health officials believe the primary vector in Hawaii’s previous Dengue outbreak was the Aedes albopictus mosquito, which is an inefficient vector of dengue. Determining where the more efficient vector, Aedes aegypti mosquito is present will help the department map out targeted vector control efforts. The aegypti mosquito is more common in countries where dengue has been established and may be responsible for maintaining a reservoir of infection that results in recurring outbreaks. It is also still present on some Hawaiian islands such as Molokai.

The State now has its own Dengue Fever laboratory and will eliminate the need to send samples to remote CDC sites. Turnaround time is reduced now to 2-3 days (37)). Also State vector control crews will continue to spray around homes when there is a suspected case of dengue to eliminate mosquitoes that could pick up the virus and infect others. This represents a continuous vigilant effort to eliminate Dengue Fever vectors as early as possible. Another vigilant effort involves always keeping aware of any occurrence of Dengue Fever. For this a Dengue Fever website has been established that continuously updates information on the virus in Hawaii and around the world.

Bioterrorism and Dengue Fever
There are a number of reasons why biological agents would be chosen as a means of terroristic attack. They can cause the maximum number of casualties, disrupt civil order and infrastructure, overwhelm government and emergency response systems, and create panic, confusion, and fear. The agents used tend to be highly pathogenic. A low dose can be very effective. They are highly infectious; the perpetrators themselves are protected with vaccines. They are also easily and quickly produced, and most are environmentally stable.

Compared with other weapons of mass destruction, biological agents are easy and inexpensive to obtain. They can affect a large area, and the effects can spread quickly to outlying areas. Biological agents are hard to detect, as the agents are odorless and colorless, and the perpetrator can escape before the effects are evident. The first symptoms are nonspecific, further delaying the detection, and once bioterrorism is identified, the public may panic and medical capabilities can be overwhelmed.

Terrorists could disseminate biological agents in several ways. They could fly a plane over a Stadium and disperse a cloud of anthrax over the crowd, and the degree of dispersion would depend on the wind speed and turbulence. They could use vectors, such as fleas and mosquitoes, or rodents. They could choose bombs, artillery shells, or missiles. They could disperse the agent through a ventilator system or add it to food and water.

Regarding Dengue Fever, Harnod and colleagues have explored the potential of Dengue Fever to be used as a bioterrorism agent. Although Dengue Fever is not transmissible by small-particle aerosols, and primary dengue causes hemorrhagic fever rarely, it still may carry great morbidity and mortality during an outbreak (38). For example, it can affect the operational abilities of military troops and Dengue has affected past military operations, dating back to the Spanish-American War, particularly the Philippines (39). Additionally, more than 90,000 cases were reported in World War II. More recently, dengue fever was the primary arboviral, or arthropod-carried, disease confirmed among U.S. military personnel in southern Somalia in 1993. During a surveillance period for Operation Uphold Democracy in Haiti in 1994, dengue fever accounted for at least 30 percent of the febrile illnesses among hospitalized US troops. Since there is no vaccine, repellents with DEET and environmental vector control are currently the only line of defense against Dengue.

Dengue Fever in civilian communities can affect the tourism economies of regions depending on this industry, create pain and suffering among citizens and affect their ability to work and be productive. Harnod, et al. (38) emphasize that it is essential to teach the medical community how to diagnose and manage dengue and dengue hemorrhagic fever and to implement an emergency contingency plan to anticipate the logistical issues of hospitalizing large numbers of patients and to outline measures for community-wide vector control activities. Public education for carrying out vector control is an essential step in control of Dengue both in natural and bioterrorism situations.
The Hawaii Dengue Fever Model Applied to Bioterrorism

Although it is impossible to predict which biological agents a terrorist might employ to attack a population, it would be ideal to have a bioterrorism prevention/action model that could deal generically with any and all biological agents. The bioterrorism acts that must be prepared for are as follows:

A. Dissemination of biological agents through the environment by terrorists, without transmission through vectors or humans. Examples would be anthrax distributed through the atmosphere or mail, or biological toxins delivered through the water supply.

B. Dissemination of a bacteria or virus through an animal or insect vector, where the human does not generally serve as a host for further spread. West Nile virus is an example.

C. Dissemination of a bacteria or virus through an animal or insect vector, where the human serves as a host for further spread by the vector, but human to human transmission does not occur. Dengue fever is an example.

D. Dissemination of a bacteria or virus possibly through an animal or insect vector initially, where the human serves as the main host for further spread with human to human transmission. SARS is an example.

Model A would be the most rapid and sudden, with prevention leaning towards environmental surveillance, and management dependent on rapid identification of the agent so correct therapy can be instituted. Models B and C may be less likely to be used by terrorists, as the epidemic takes time to develop and does not give them the type of rapid event that would dominate the news. Prevention would be aimed at controlling the vector. Model D can be devastating as witnessed with SARS. The difficulty for such agents as a bioterrorism agent is controlling the epidemic once it starts to spread.

The intent of the terrorists needs to be considered. Mortality is usually the goal which strikes the most fear. However, a moderately debilitating, rarely fatal illness can contribute to significant morbidity for the target population. This is particularly applicable to military units, where timely use of such agents can be equally as devastating as mortality. Therefore, depending on the situation, even less deadly agents must be considered to be bioterroristic agents. This concept conforms with the CDC’s ranking of bioterroristic agents from A to C.

In the case of Dengue Fever, a vector borne disease, the Hawaii model of core capabilities is one built on experience and one that will prove successful should Dengue Fever emerge again in Hawaii, either through natural or intentional means. In terms of crippling the economy of Hawaii, which is tied to tourism, and affecting military troops stationed in Hawaii, an intentional release of Dengue Fever into the Hawaiian communities could be an attractive strategy for bioterrorists, especially if they wanted to impact the economy by decreasing tourism.
The basic core strengths and capabilities of the Hawaii Dengue preparedness model can be summarized as follows:

- Staff members well experienced with Dengue Fever outbreaks
- *In-state* laboratory facilities for confirming Dengue Fever
- Long-term dengue surveillance system statewide
- Statewide mosquito population surveys
- Ongoing vector control efforts
- Procedures/experience and ongoing efforts with public education (e.g., mosquito eradication) via media, web, etc.
- Experience with physician/ER/Hospital advisories regarding Dengue Fever
- Procedures for tourist education/repellent dissemination, road closures
- Ongoing monitoring of Dengue Fever outbreaks locally and worldwide
- Mapping/modeling technologies locally available
- Constant state of alertness/suspicion for Dengue cases among population and healthcare practitioners.

How do these capabilities relate to the US Government’s assessment of how well the nation is prepared (or is continuing to prepare) for a bioterrorism emergency? In the Public Health Improvement Act that was passed in 2000 (40), Congress directed the Government Accounting Office (GAO) to examine preparedness for a bioterrorist attack among hospitals as well as state and local public health agencies. GAO found that preparedness varied across state and local jurisdictions and deficiencies in preparedness remain in every city (41). Deficiencies occurred in communication and coordination elements, workforce shortages, inadequacies in disease surveillance and laboratory systems and lack of compatible communications systems. Some elements, such as those involving coordination efforts and communications systems, were being addressed more readily, whereas others, such as infrastructure and workforce issues were more resource-intensive and more difficult to address. Cities with more experience in dealing with a public health emergency were generally better prepared for a bioterrorist attack than other cities.

GAO also reported that progress toward bioterrorism preparedness among the 50 states is very slow. No state met all the benchmarks by the due date. However, with progress that has been made, in general the states are better off now than they were prior to the cooperative agreement programs through which funds were distributed (42). Still, in another reports, GAO has found that most urban hospitals have emergency plans but lack certain capacities for bioterrorism response (43). Proper equipment is in short supply for a bioterrorism event. Larger hospitals had more plans in place, training and drills than smaller healthcare facilities.

When GAO looked at the SARS outbreak and assessed infectious disease preparedness in the USA, they found that improvements to public health capacity are needed for responding to SARS, bioterrorism and emerging infectious diseases (44). A state or city that experienced a major health threat before is more prepared for dealing with an infectious disease. Hawaii, with its latest experience, seems to
have reached a higher level being much better prepared now, at least for a vector-born event, which begs the question: Does it really take a major health crisis to improve bioterrorism or infectious disease preparedness? Perhaps not, but a crisis does seem to affect and accelerate the timing of events regarding having a viable plan in place and acquiring critical facilities and equipment.

Conclusion

As stated by the GAO, the United States is clearly not fully prepared to deal with a bioterrorism event. Although progress has been made, it is slower than anticipated. A key point expressed by GAO is that states and cities that have experienced major health crises are better prepared overall than those who have not. As experience seems to hold the key to preparedness, transfer of knowledge through reports such as this one and communication through conferences would be instrumental in enhancing awareness of the problem. The fact that Hawaii’s experience came during a synchronous terroristic national attack provides one with a deeper insight into the issues that need to be addressed.

References


Bioterrorism Preparedness: Clinical Trials Center in Infectious Disease
June 15-18, 2004
Telehealth Research Institute (TRI)
University of Hawaii, John A. Burns School of Medicine
Co-Hosts:
Armed Forces Research Institute of Medical Sciences (AFRIMS)
Royal Thai Army Medical Department

CONFERENCE OVERVIEW

In an era of dramatically increased travel, rapid natural (and even engineered) manipulation of infectious agents, as well as security concerns related to bioterrorism, a new means of testing and evaluation for vaccine and antibiotic therapy is desperately needed. While both the DOD and NIH have been long focused on this problem, there remains significant difficulty in providing timely research when the majority of affected populations for these diseases live on foreign soil. To address this problem, the ideal scenario would consist of a foreign-based Clinical Trials center fully integrated with the most advanced technologies in broadband medical networking and clinical informatics assuring local and regional access to affected patient populations and seamless integration with state of the art US research methods.

Beyond technology, new models of integrating government agencies, non-governmental organizations and private industry could be tested in such a setting. A US certified laboratory with a large animal lab including primates would be a necessity to support such a clinical trials unit, as well as a close working relationship with a friendly host nation’s medical personal. The Center should also have a major affiliation with one or several US universities conducting both basic science and clinical research at the Center. The Center should also have broadband links to the US for transfer of data, and collaboration with ongoing genomics and proteomics researchers in the field.

Through existing grants and relationships, a partnership to address this problem is emerging between the University of Hawaii (UH), Phramongkutklao (PMK) Medical Center, and the Armed Forces Research Institute of Medical Science (AFRIMS). These two organizations share the same campus in Bangkok, Thailand. Other partnerships in the region are also possible for UH through this association.

The objectives of this meeting are to: 1) further define the problem, 2) discuss laboratory capabilities in the region which are integral to such a partnership, while providing important infrastructure for related disease surveillance and outbreak management, 3) further define the partnership between UH-PMK-AFRIMS, 4) explore other organizations that could partner with this consortium, and 5) identify potential funding sources for such a Center.
# Agenda

**BioTerrorism Preparedness: Clinical Trials in Infectious Disease**  
Bangkok, Thailand  
June 15 -18, 2004

## Day 1 – Tuesday, June 15, 2004

<table>
<thead>
<tr>
<th>Location</th>
<th>Time</th>
<th>Topic</th>
<th>Presenter</th>
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<tbody>
<tr>
<td>Four Seasons,</td>
<td>1300-1500</td>
<td>Program review: Final coordination with RTA, AFRIMS, hotel staff, schedule modification</td>
<td>Program Committee</td>
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<tr>
<td>Montathip II</td>
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<td>Board Room</td>
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<tr>
<td>Four Seasons</td>
<td>1500 - 1800</td>
<td>Registration; Speaker Ready Room Open</td>
<td>All Participants; Speakers</td>
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<tr>
<td>Four Seasons,</td>
<td>1800 - 1930</td>
<td>Welcome Reception! Networking, group discussions.</td>
<td>All Participants</td>
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## Day 2 – Wednesday, June 16, 2004

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<tr>
<td>Four Seasons,</td>
<td>Breakfast</td>
<td>Breakfast on own</td>
<td>All Participants</td>
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<tr>
<td>Biscotti</td>
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<tr>
<td>Four Seasons,</td>
<td>0900-1100</td>
<td>Planning for 2005 conference Speaker Ready Room Open</td>
<td>Program Committee</td>
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<td>Montathip II</td>
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<tr>
<td>Boardroom, Lobby</td>
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<td>level</td>
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<tr>
<td>Four Seasons,</td>
<td>1100 - 1130</td>
<td>Registration</td>
<td>Lawrence Burgess, M.D.</td>
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<td>Montathip II</td>
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<tr>
<td>Boardroom, Lobby</td>
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<td></td>
<td>Gregory Mogel, M.D.</td>
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<td>level</td>
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<tr>
<td>Four Seasons</td>
<td>1130 - 1200</td>
<td>Luncheon Meeting: Welcome, Administrative Announcements, Conference Overview</td>
<td>COL Carl Mason</td>
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<td>COL Suwicha Tim</td>
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<td>Four Seasons</td>
<td>1200 - 1250</td>
<td>Dengue Fever: Update 2004</td>
<td>Duane Gubler, ScD</td>
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<tr>
<td>Four Seasons</td>
<td>1250 - 1300</td>
<td>Break</td>
<td>All Participants</td>
</tr>
<tr>
<td>Meet in</td>
<td>1300 - 1330</td>
<td>Travel to Phramongkutklao (PMK)</td>
<td>All Participants</td>
</tr>
<tr>
<td>Time</td>
<td>Location</td>
<td>Activity</td>
<td>Participants</td>
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<tr>
<td>1330 - 1600</td>
<td>PMK Medical Center</td>
<td>Welcome to PMK, Tour of facilities - Presentations of ongoing UH-PMK collaborations (THAI-HI project, Trial in Neurological Complications of Infectious Disease, Bioterrorism Preparedness-Clinical Trials Center)</td>
<td>All Participants</td>
</tr>
<tr>
<td>In transit</td>
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<td>Travel to Four Seasons</td>
<td>All Participants</td>
</tr>
<tr>
<td>1600 - 1630</td>
<td>Four Seasons</td>
<td>Informal discussions, free time</td>
<td>All Participants</td>
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<tr>
<td>1630 - 1830</td>
<td>Four Seasons, Montathip II Conference Room, Lobby level</td>
<td>Networking reception, THAI Set dinner meeting: Introduction of THAI, US, Hawaii guests of honor</td>
<td>All Participants</td>
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<tr>
<td>1830 - 2130</td>
<td>Four Seasons</td>
<td>Networking reception, THAI Set dinner meeting: Introduction of THAI, US, Hawaii guests of honor</td>
<td>All Participants</td>
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### Day 3 – Thursday, June 17, 2004

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<tr>
<td>Four Seasons, Biscotti</td>
<td>0630 - 0800</td>
<td>Breakfast on own; Informal discussions, Conference Room Open</td>
<td>All Participants</td>
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<tr>
<td>Meet in Lobby, Four Seasons AFRIMS</td>
<td>0800 - 0830</td>
<td>Travel to AFRIMS</td>
<td>All Participants</td>
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<tr>
<td>In transit</td>
<td>1130 - 1200</td>
<td>Travel to Bumrungrad Hospital</td>
<td>All Participants</td>
</tr>
<tr>
<td>Bumrungrad Hospital</td>
<td>1200 - 1500</td>
<td>Introduction to Bumrungrad Hospital; Tour of facilities, Clinical Trials Center</td>
<td>All Participants</td>
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<tr>
<td>Four Seasons</td>
<td>1530 - 1830</td>
<td>Informal discussions, free time</td>
<td>All Participants</td>
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<tr>
<td>Four Seasons, Madison, Lobby level, off of courtyard</td>
<td>1830 - 2130</td>
<td>Planning dinner meeting: 2004 Conference discussion, plans for 2005; Speakers suggestions for JCRC</td>
<td>Speakers, Program Committee</td>
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### Day 4 – Friday, June 18, 2004

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<tr>
<td>Four Seasons, Montathip II Boardroom, Lobby level</td>
<td>0745 - 0900</td>
<td>Breakfast Meeting: University of Hawaii and Research in Infectious Diseases</td>
<td>Duane Gubler, ScD Director, Asia-Pacific Institute of Tropical Medicine and Infectious Diseases, Univ. of Hawaii</td>
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<tr>
<td>Montathip II Boardroom</td>
<td>0900 - 1000</td>
<td>Industry Sponsored Clinical Trials in Asia</td>
<td>Rick Yanagihara, MD, MPH Dept. of Pediatrics, Univ. of Hawaii</td>
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<tr>
<td>Montathip II Boardroom</td>
<td>1000 - 1015</td>
<td>Break</td>
<td>Robert Teoh, MSBS MD FRCP VP Clinical Operations, Asia-PPD</td>
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<tr>
<td>Montathip II Boardroom</td>
<td>1015 - 1245</td>
<td>UH-AFRIMS-PMK Clinical trials, alone or in collaboration with others: problem definition, constructing relationships, funding possibilities</td>
<td>Lawrence Burgess, M.D. University of Hawaii, John A. Burns School of Medicine (JABSOM) Gregory Mogel, M.D. TATRC, USAMRMC, Ft. Detrick, MD</td>
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<tr>
<td>Montathip II Boardroom</td>
<td>1245 -1300</td>
<td>Concluding Remarks</td>
<td>All Participants</td>
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<tr>
<td>1300</td>
<td>Conference Analysis, Wrap-up</td>
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<td>1300-1600</td>
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**Program Committee**
Clinical Trials in Emerging Infectious Diseases.

"Industry sponsored clinical trials in Asia"
## Asian Economies

<table>
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<tr>
<th>Country</th>
<th>Population (million)</th>
<th>GDP (US $,000)</th>
<th>Doctors (per 1,000)</th>
<th>Health Care Spending (% of GDP)</th>
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<td>Taiwan</td>
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<td>6.2</td>
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<td>2</td>
<td>0.4</td>
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<td>India</td>
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<td>0.4</td>
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<tr>
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USA

|   | 275 | 34  | 2.7  | 13   |

*PPD®
Strategic solutions for a decided advantage®*
Industry sponsored clinical drug trials: Why Asia?

- Patient availability
- Higher patient: doctor ratio
- Well trained & motivated investigators
- Fewer & large referrals centers / study sites
  - large specific patient groups per specialist
- Specific therapeutic indications
  - infectious diseases: HBV, HIV, malaria, CAP
Asia - competitive advantage
Patients

- Large patient population - but
- Large target patient population per investigator
  - large regional referral centres
  - fewer doctors / specialists per head of population than in US/EU
- Treatment-naive patients
- Less competition for patients in clinical trials

PPD®
Strategic solutions for a decided advantage®
Asia - competitive advantage
Investigators

- Investigator participation driven by interest in disease, research & publication. Investigators fees go to research, not investigator salaries - less incentive for fraud.

- Excellent follow-up: less drop-outs compared to US/EU eg schizophrenia, HBV
Asia - competitive advantage
Cost efficient

- Lower investigator fees
- Low or absent institutional fees
- Higher patient recruitment per site - into lower study management costs
- Shorter patient recruitment time - reduced costs
- Generally lower cost environment - lower charge-out rates
- But caveats eg oncology

PPD® Strategic solutions for a decided advantage®
Industry sponsored clinical trials in Asia - quality & usable data

- Asian study sites audited by US FDA & Japanese KIKO
- Study sites, CRO offices audited by US & EU based clients
- Data accepted by EMEA
- Quality of Asian data as good as from US / EU:
  - based on # data queries per case report form
Industry sponsored clinical trials in Asia - quality & usable data

- ICH GCP guidelines accepted *
- Local GCP guidelines based on ICH
  - Singapore - minors. Korea - cancer
- Ethics committees - properly constituted -
  (some require admin improvements).
- Source document verification - documents available for monitoring & audit
- Patient informed consent - genuine & fully informed. (Care with incentives, no unintended coercion)

PPD Strategic solutions for a decided advantage®
Industry Sponsors in Asia

- Big Pharma
- Biotech
- Medical Appliance

- NIH

- (academic research - not for profit)
Industry sponsored clinical trials in Asia - study sites

- Usually only academic centres or large regional hospitals - rarely small hospitals or general practice clinics
- Clinical trial coordinators essential
  - investigators little time for completion of case report form
  - in absence of coordinators, hire or pay investigators to hire (in China, hire hospital doctors to perform task)
Clinical trials in Asia - Ethics committees / IRB

- Ethics committees / institutional research boards
  - usually properly constituted, SOPs, minutes, audits etc as per ICH GCP?

- **Central IRBs** - in some countries but no professional / regional IRBs
  - but which IRB is responsibility for patient safety, rights?

- Knowledge expertise to review new therapies? eg gene therapy

PPB Strategic solutions for a decisive advantage
Clinical trials in Asia - Study sites

- Site management organizations (SMO) common in Japan & India, rare elsewhere
- Clinical contract research organizations (CRO) common
- Academic SMO / CRO in Hong Kong, Singapore, Taiwan, Australia (like Duke CRC) - for profit?
- Regional / local networks of clinical investigators - eg oncology, stroke
Clinical trials in Asia - Issues

• Regulatory approval - long
  – Singapore, Hong Kong: 3 - 4 mths
  – Thailand, Taiwan: 4 - 6 mths
  – India, India: 6 - 12 mths

• Translation - variable requirements of - IB, protocol synopsis, patient informed consent.

• Investigator / institution contracts

• Patient Indemnity / insurance *

PPD®
Strategic solutions for a decided advantage®
Clinical trials in Asia - Issues

- Pharmacogenomics
  - protocols do not always define exactly what will be studied
  - ownership of intellectual property
  - national ‘rights’ lost eg as per drugs derived from local herbs

- Export of biological samples
  - difficult in some countries
Clinical trials in Asia - Laboratory Issues

• Central labs - few
• Courier between countries - very expensive
• Courier within country - cold chain
• Lab accreditation by US or international organizations expensive but more widespread

PPD®
Strategic solutions for a decided advantage®
Asia - cultural differences & clinical research

• Confucian doctor - patient relationship

• Patients less inclined to question / doubt physician
  – incidence of adverse events & serious adverse events - ‘look for them’

• Genuine patient informed consent

• Cancer: family decision whether to inform patient of diagnosis.
Asia - cultural differences & clinical research

- 'Guinea pig' misconception of clinical research
- 'Standard of care' eg hepatocellular carcinoma
- High dose anti-viral therapy eg HIV
- No coercion to join study - alternative to non participation in study?
Diseases studied

- Oncology - hepatocellular carcinoma, NSCLC, pancreatic cancer
- Infectious diseases - HBV, opportunistic infections, AIDS, community acquired pneumonia, malaria
- Degenerative diseases - dementia, stroke, coronary stents
- Metabolic diseases - diabetes, hypercholesterolaemia
- Vaccines - HBV
PPD Asia
Office locations

- China: Beijing
- China: Hong Kong
- India: Mumbai
- Singapore
- Taiwan: Taipei
- Thailand: Bangkok

- Korea: Seoul (Q3, 2004).

PPD®
Strategic solutions for a decided advantage®
PPD Asia - staff

- PPD Asia - clin ops since 1998
- Quality, experienced senior staff
- > 20 yrs in academia, pharma & CRO experience in Asia/US/Europe
- Solid reputation with - investigators, opinion leaders, regulatory authorities
- Staff are local nationals - stable work force
PPD Asia - staff

• Local knowledge
  – culture, language, committed to ethical behavior & GCP

• Trained & experienced staff based in each country: geographically & culturally close to sites - ensures careful supervision of sites
  – support adherence to protocol,
  – ensure SAE are reported
PPD - Global Standards

• ICH - GCP standards
  – plus local GCP guidelines

• Global PPDs SOPs

• Asian CRAs trained at PPDs global Foundation course in USA.
The Global Resurgence of Epidemic Dengue/Dengue Hemorrhagic Fever

Duane J Gubler
Asia-Pacific Institute of Tropical Medicine and Infectious Diseases
John A Burns School of Medicine, University of Hawaii at Manoa
Honolulu, Hawaii
Dengue Viruses

Family: Flaviviridae
Genus: Flavivirus
Serotypes: Den-1
            Den-2
            Den-3
            Den-4
Transmission and Maintenance Cycles of Dengue Viruses

Africa = Aedes (Diceromyia )
Aedes (Stegomyia )

Asia = Aedes (Finlaya )
Aedes (Stegomyia )

Americas = Aedes Sp.?
Differential Diagnosis of Dengue and DHF

- Influenza
- Measles
- Rubella
- Malaria
- Typhoid Fever
- Leptospirosis
- Rickettsial infections
- Bacterial sepsis
- Other viral hemorrhagic fevers
Resurgence of Dengue/ Dengue Hemorrhagic Fever

- Expanding Geographic Distribution
- Increased Epidemic Activity
- Hyperendemicity
- Emergence of DHF
Epidemic Dengue Hemorrhagic Fever in Asia

1950-1970

1980-2004

1970-1980
Total Mean Annual Number of DHF Cases Reported Thailand, Indonesia, and Vietnam, by Decade

Provisional Data: reports for only 8 years.
Aedes aegypti Distribution in the Americas

1930's

1970

2004
Dengue Hemorrhagic Fever in the Americas by Decade

Data: PAHO To Oct 2003
The Emergence of Dengue Hemorrhagic Fever in the Americas

Prior to 1981

1981-2004
Autochthonous Dengue in the United States

<table>
<thead>
<tr>
<th>Year</th>
<th>Location</th>
<th>No. Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>1945</td>
<td>Louisiana</td>
<td>143</td>
</tr>
<tr>
<td>1980</td>
<td>Texas</td>
<td>27</td>
</tr>
<tr>
<td>1986</td>
<td>Texas</td>
<td>9</td>
</tr>
<tr>
<td>1995</td>
<td>Texas</td>
<td>7</td>
</tr>
<tr>
<td>1997</td>
<td>Texas</td>
<td>3</td>
</tr>
<tr>
<td>1998</td>
<td>Texas</td>
<td>1</td>
</tr>
<tr>
<td>1999</td>
<td>Texas</td>
<td>17</td>
</tr>
<tr>
<td>2001</td>
<td>Hawaii</td>
<td>122</td>
</tr>
</tbody>
</table>
Imported and Local Dengue Cases in Hawaii, 2001

Source: Hawaii DOH/Epidemiology Branch
Dengue 1 Phylogeny

15 isolates from Hawaii residents - Den-1

American Genotype

Pacific Genotype

DEN. Mil Trop Med Inf. 2002; p. 16
Epidemic Dengue Fever in Hawaii, 2001

Conclusions

- **Outbreak**
  - Smoldering vs. explosive transmission
  - Mild illness
  - Geographic spread
- **Mosquito Vectors**
  - *Aedes albopictus*
Countries in the World Reporting DHF cases, 1950 – 2000 (cumulative)*

*Source: Dr. A.B. Knudsen, WHO
Dengue/dengue hemorrhagic fever, average annual number of cases reported to WHO, 1955-2001
Global Distribution of Dengue Virus Serotypes, 1970
Global Distribution of Dengue Virus Serotypes, 2004
Hyperendemicity

Increased Transmission and Movement of Viruses

Increased Probability of Virulent Strain Selection or Introduction

Increased Probability of DHF

Increased Probability of Secondary Infection

Increased Probability of Immune Enhancement
Pathogenesis of Dengue Hemorrhagic Fever

Summary and Conclusions

• Viral and Immunopathogenesis
  – Not mutually exclusive
  – Both are important

• Only certain virus strains can cause the immunopathogenetic cascade of events leading to increased vascular permeability

• Other Viral Pathogenetic Mechanisms
  – Encephalopathy/encephalitis
  – Hepatic failure
  – Severe hemorrhage
THE ICEBERG CONCEPT OF DENGUE IN RELATION TO THE TOTAL NUMBER OF DENGUE INFECTION

Spectrum of Clinical Illness

Severe Dengue
Classical Dengue Fever
Mild Febrile Illness
Inapparent Infection
World Distribution of Dengue - 2004

- Areas infested with Aedes aegypti
- Areas with *Aedes aegypti* and dengue epidemic activity
Global Dengue Disease Burden

<table>
<thead>
<tr>
<th>Description</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. dengue cases/year</td>
<td>50-100 million</td>
</tr>
<tr>
<td>No. DHF/DSS cases/year</td>
<td>500,000</td>
</tr>
<tr>
<td>No. deaths/year</td>
<td>20-25,000</td>
</tr>
</tbody>
</table>

Data from WHO
Economic Impact of Dengue/
Dengue Hemorrhagic Fever

Disability Adjusted Life Years (DALYs)

• Same order of Magnitude
  – Malaria
  – Tuberculosis
  – Hepatitis
  – Sexually Transmitted Diseases
  – Childhood Cluster
  – Tropical Cluster
Factors Responsible for Increased Epidemic Dengue/Dengue Hemorrhagic Fever

- Complacency
  - Policy decisions
  - Decreased resources
  - Decay in infrastructure
- Population Growth
  - Unplanned Urbanization
  - Changing Lifestyles
- Modern Transportation
- Lack of Effective Mosquito Control
- Climate Change?
Prevention and Control of Dengue/Dengue Hemorrhagic Fever

- Mosquito Control
- Vaccines
Summary Status of Dengue Vaccine Development

- No licensed vaccine available
- Effective dengue vaccine must be tetravalent
Summary Status of Dengue Vaccine Development

- Live-attenuated dengue vaccine, Mahidol University, Thailand
  - Commercialized by Aventis-Pasteur
  - Recent field trials – Thailand
  - Future field trials
- U.S. Army live-attenuated vaccine
  - Clinical trials
  - GalaxoSmithKline is commercial partner
- NIH/FDA 3’ deletion mutation attenuation
  - NIH live-attenuated candidates based on naturally attenuated strains
### DEN-2 PDK-53-Based Chimeric DEN Viruses

<table>
<thead>
<tr>
<th>5'</th>
<th>C</th>
<th>prM</th>
<th>E</th>
<th>NS1</th>
<th>2A</th>
<th>2B</th>
<th>NS3</th>
<th>4A</th>
<th>4B</th>
<th>NS5</th>
<th>3'</th>
</tr>
</thead>
<tbody>
<tr>
<td>▲</td>
<td>△</td>
<td>△</td>
<td>△</td>
<td>△</td>
<td>△</td>
<td>△</td>
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<td>△</td>
<td>△</td>
<td>△</td>
<td>△</td>
</tr>
</tbody>
</table>

**DEN-2 PDK-53 Genome**

<table>
<thead>
<tr>
<th>prM</th>
<th>E</th>
<th>DEN-2/1 = DEN-1 16007 (prM/E)</th>
</tr>
</thead>
<tbody>
<tr>
<td>prM</td>
<td>E</td>
<td>DEN-2/3 = DEN-3 16562 (prM/E)</td>
</tr>
<tr>
<td>prM</td>
<td>E</td>
<td>DEN-2/4 = DEN-4 1036 (prM/E)</td>
</tr>
</tbody>
</table>

▲ = Dominant 5’NC-57 and NS1-53 attenuating mutations

△ = Minor prM-29, NS2A-181 and NS4A-75 mutations

* = DEN-2 PDK-53, NS3-250-Glu variant
Summary Status of Dengue Vaccine Development

- Infectious cDNA clone based vaccine
  - DEN-2 PDK-53 - CDC
  - Yellow Fever 17D - Acambis
  - DEN-4 - NIH
- Naked DNA vaccine – Navy, CDC
Summary Status of Dengue Vaccine Development

Pediatric Dengue Vaccine Initiative

• Goals
  – Facilitate public private partnerships
  – Accelerate development and introduction of dengue vaccines
Asia-Pacific Institute of Tropical Medicine and Infectious Diseases
John A Burns School of Medicine, University of Hawaii at Manoa
Joint Clinical Research Center (JCRC)
AFRIMS-PMK-UH

Lawrence P.A. Burgess, MD
Associate Dean for Govt. Affairs
Dir. of Telehealth Research Institute
University of Hawaii
John A. Burns School of Medicine
Co-Hosts

- AFRIMS: COL Carl Mason, LTC Mike Lewis
- Royal Thai Army Medical Department: COL Tim Chitpatima, PhD COL Parinya Thavichaigarn, MD
- Funding Agency: TATRC, Greg Mogel, MD, government contracting representative (COR).
Early Groundwork

- THAI-HI project. Initial investment by Pacific Telehealth and Technology HUI, to support regular videoteleconferencing between Tripler AMC Hawaii, and PMK Medical Center.
- PIs: COLs Ben Berg, Dale Vincent, Tim Chitpatima
- Follow-on foundation grant through UH, ending October ‘04 (PI: Dr. Burgess).
ID Focus

• LTC Jerome Kim (UH Professor)
• Built ID focus in separate partnership with AFRIMS-PMK, COL Chitpatima collaborating.
• Will be stationed at AFRIMS for 3 years.
• Co-investigator initiating UH clinical trial to study neuro-complications of HIV-AIDS at PMK.
ID Focus

• Dr. Burgess (PI): funding through Telemedicine and Advanced Technology Research Center (TATRC), Ft. Detrick, MD, for Bioterrorism Preparedness ID

• Year 2 award will focus on forming JCRC between AFRIMS-PMK-UH and other partners.
Purpose of TATRC Grant

- Cross classic funding lines to provide
- a strong university collaboration
- with government organizations.
- Provide infrastructure dollars
  (equipment, personnel, pilot
  projects) to develop the JCRC.
Other UH Involvement

• Duane Gubler, ScD: Dir. Asia-Pacific Institute of Tropical Medicine and Infectious Diseases.
• Ric Yanagihara, MD, MPH: RCMI Director UH, senior ID researcher.
• Cecilia Shakuma, MD: HIV researcher UH, collaborator with Dr. Kim
AFRIMS

- COL Carl Mason: Commander, AFRIMS.
- LTC Mike Lewis: XO, Dir. DoD Global Emerging Infections Surveillance and Response System (GEIS).
Royal Thai Army (RTA) Medical Department

- Surgeon General, LTG Pravit Tanprasert, MD, recently named directors of JCRC after awarding of the JCRC TATRC grant.
- COL Tim Chitpatima: Director
- COL Parinya Thavichaigarn: Clinical Director.
Other Collaborators

- Clinical Research Organizations (CROs) could be supportive in early stages.
- Robert Teoh, MD, of PPD, has extensive experience in this area.
Conference Goals

- Better understanding of partners strengths and weaknesses.
- Develop road map to develop and grow the JCRC.
Collaborative Research and Training Opportunities in Emerging Infectious Diseases

Richard Yanagihara, M.D., M.P.H.

Professor, Departments of Pediatrics, Tropical Medicine and Public Health Sciences and Epidemiology
John A. Burns School of Medicine, University of Hawai‘i at Manoa

Bioterrorism Preparedness:
Clinical Trials Center in Emerging Infectious Diseases
June 15-18, 2004 Bangkok, Thailand
University of Hawai'i System: 10 Statewide Campuses

University of Hawai'i at Manoa
University of Hawai'i at West Oahu
Kapolei Community College
Kapi'olani Community College
Leeward Community College
Windward Community College

University of Hawai'i at Hilo
Hawaii Community College

Kauai Community College
John A. Burns School of Medicine

Vision of Governor John A. Burns
- If Hawaii was to have a great University, it needed to have a medical school
- Established as a two-year school in 1967 and a four-year school in 1973; first M.D. graduates in 1975

Distinguishing Features
- One of the most ethnically diverse medical schools in the Nation
- Excellence in medical education: problem-based learning curriculum
- Excellence in research: reproductive biology, gerontology, infectious diseases
Asia-Pacific Institute of Tropical Medicine and Infectious Diseases

Pacific Center for Emerging Infectious Diseases Research

Pacific Rim Biodefense Center

Pacific Asia Center for Infectious Disease Ecology

Pacific Center for Vaccine and Gene Therapy Research

Pacific Center for AIDS Research

RCMI Retrovirus Research Lab

RCMI HIV Immunology and Vaccine Core

Hawaii ACTU

Hawaii NeuroAIDS SNRP

Hawaii AITRP (under review)
Organizational Structure of the Asia-Pacific Institute of Tropical Medicine and Infectious Diseases

Board of Regents

President of University of Hawai'i System

Chancellor of University of Hawai'i at Mānoa

Dean of John A. Burns School of Medicine

Nine additional Campuses

Other Level-V Units

Basic Science Departments

Pacific Center for Vaccine and Gene Therapy Research

Pacific Asia Center for Infectious Disease Ecology

Pacific Rim Biodefense Center

Clinical Departments

Pacific Center for AIDS Research

Pacific Center for Emerging Infectious Diseases Research
Organizational Structure of the Pacific Center for Emerging Infectious Diseases Research

Executive Board
E.C. Cadman (JABSOM)
D.J. Gubler (JABSOM)
D. Easa (JABSOM)
C.-W. Vogel (CRCH)
C.D. Boyd (PBRC)
D.O. Smith (SOEST)

Pacific Center for Emerging Infectious Diseases Research
R. Yanagihara (JABSOM)
Director

External Advisory Committee
C.J. Peters (U Texas Galveston)
K.K. Holmes (U Washington Seattle)
D.E. Griffin (Johns Hopkins Baltimore)
M.W. Cunningham (U Oklahoma)

Administrative and Mentoring Core
R. Yanagihara (JABSOM)
V.R. Nerurkar (JABSOM)
G.S.N. Hui (JABSOM)
M.T. Goodman (CRCH)
P.V. Effler (DOH)

Technical Support Core
V.R. Nerurkar (JABSOM)

Project 1
Natural History of HPV in Heterosexual Men
B.Y. Hernandez (CRCH)
L.F. Xi (U California)

Project 2
Immunopathogenesis of Dengue
A. Imrie (JABSOM)
F.A. Ennis (U Massachusetts)
A.L. Rothman (U Massachusetts)

Project 3
Molecular Epidemiology of Group A Streptococci in Hawai‘i
G. Erdem (JABSOM)
E. Kaplan (U Minnesota)
Mission:
To serve as a center of excellence for research and training in tropical infectious diseases and as a regional reference center for the diagnosis and control of new, emerging and re-emerging microbial threats, which are relevant to the peoples of the Asia-Pacific region.
Specific Aims:

1. Build institutional capacity by mentoring a cadre of promising young faculty to conduct research on infectious diseases of medical importance to the Asia-Pacific region.

2. Improve research competitiveness by enhancing the capacity for mentoring and expanding the capability of the technical support infrastructure.

3. Diversify the research breadth and trans-disciplinary scope of the Center through international collaborations and targeted recruitment and retention of funded faculty with complementary expertise.
Pacific Center for Emerging Infectious Diseases Research

Vivek R. Nerurkar, Ph.D.
Professor, Department of Tropical Medicine and Medical Microbiology,
John A. Burns School of Medicine

George S.N. Hui, Ph.D.
Professor, Department of Tropical Medicine and Medical Microbiology,
John A. Burns School of Medicine

Marc Goodman, Ph.D., M.P.H.
Professor, Cancer Etiology Program,
Cancer Research Center of Hawai‘i

Paul V. Effler, M.D., M.P.H.
Chief, Division of Disease Outbreak Control,
State Department of Health
External Advisory Committee

Diane E. Griffin, M.D., Ph.D.
Professor and Chair,
W. Harry Feinstone Department of Molecular Microbiology and Immunology,
Johns Hopkins Bloomberg School of Public Health,
Baltimore, Maryland

King K. Holmes, M.D., Ph.D.
Director, Center for AIDS and STD,
Chief, Infectious Diseases, Harborview Medical Center,
University of Washington School of Medicine,
Seattle, Washington

Madeleine W. Cunningham, Ph.D.
George Lynn Cross Research Professor,
Department of Microbiology and Immunology,
University of Oklahoma Health Sciences Center,
Oklahoma City, Oklahoma

Clarence J. Peters, M.D.
Professor,
Departments of Microbiology and Immunology and Pathology,
University of Texas Medical Branch,
Galveston, Texas
# Pacific Center for Emerging Infectious Diseases Research

## Administrative and Mentoring Core

### Administration
- Research Seminar Series
- Evaluation Plan

### Mentoring
- Mentoring Plan

### Development
- Pilot Project Program
- Recruitment Plan
- Strategic Plan

## Technical Support Core

### Molecular Biology and Immunology Core Facility
- Flow cytometry
- Real-time PCR

### Biostatistics and Bioinformatics Core Facility
- BSL-3 Containment Facility
Brenda Y. Hernandez, Ph.D., M.P.H.
Assistant Researcher, Cancer Etiology Program,
Cancer Research Center of Hawai‘i

Molecular Epidemiology and Natural History of Human Papillomavirus Infection in Heterosexual Men

Allison Imrie, Ph.D.
Assistant Professor, Department of Public Health Sciences and Epidemiology, John A. Burns School of Medicine

Immunopathogenesis of Dengue Virus Infection

Guliz Erdem, M.D.
Assistant Professor, Department of Pediatrics,
John A. Burns School of Medicine

Molecular Epidemiology and Adhesion Properties of Group A Streptococci in Relation to High-Incidence Acute Rheumatic Fever in Hawai‘i
Strategic Plan

• Target recruitment and retention of promising, extramurally funded faculty who possess complementary expertise

• Expand and diversify the research breadth and trans-disciplinary scope to include international field sites in southeast Asia

• Expand collaborative partnerships and resource sharing with the State Department of Health and Department of Defense

• Integrate the infrastructure and technical services for infectious diseases research, particularly in the areas of biostatistics, bioinformatics, computational biology, information technology and metabolomics

• Improve laboratory and research-support environment, with an aim toward upgrading and centralizing certain laboratories and technical operations

• Develop NIH-funded training programs in infectious diseases and international health, with an additional aim of establishing a distributed campus for public health research and education in the Asia-Pacific region
Opportunities and Outcomes

Clinical and basic science collaborative research in new, emerging and re-emerging infectious diseases of regional importance

Sharing of resources
Complementation of expertise

Joint publications

Joint NIH grant applications for research and training

INTERNATIONAL COLLABORATIONS IN INFECTIOUS DISEASE RESEARCH (ICIDR)

GLOBAL INFECTIOUS DISEASE RESEARCH TRAINING PROGRAM AWARD

NIAID INTERNATIONAL RESEARCH IN INFECTIOUS DISEASES (IRID) R03 PROGRAM

RESEARCH SUPPLEMENTS FOR UNDERREPRESENTED MINORITIES

CHALLENGE GRANTS: BIODEFENSE PRODUCT DEVELOPMENT
INTERNATIONAL COLLABORATIONS IN INFECTIOUS DISEASE RESEARCH (ICIDR)

RELEASE DATE: April 23, 2004
RFA: RFA-AI-04-017
EXPIRATION DATE: October 14, 2004

Department of Health and Human Services (DHHS)
COMPONENT OF PARTICIPATING ORGANIZATION:
National Institute of Allergy and Infectious Diseases (NIAID) (http://www.niaid.nih.gov)

LETTER OF INTENT RECEIPT DATE: September 13, 2004
APPLICATION RECEIPT DATE: October 13, 2004

PURPOSE OF THIS RFA

The goals of the NIAID ICIDR program are to:
• support high-quality, collaborative research that will lead to or result in prevention, amelioration, and/or improved treatment of tropical infectious diseases caused by protozoa and helminth parasites, as well as bacteria and viruses identified as NIAID Category A, B and C priority pathogens;
• increase relevant research experience for both U.S. and foreign investigators;
• facilitate and enhance scientific linkages between U.S. and foreign investigators to enhance the independent research capacity of the collaborating foreign institutions and strengthen their scientific infrastructure for further international collaborative arrangements.

NIH multi-project cooperative agreement (U19) ($800,000 direct costs per year) and single project cooperative agreement (U01) ($400,000 direct costs per year) "assistance" mechanisms
GLOBAL INFECTIOUS DISEASE RESEARCH TRAINING PROGRAM AWARD

RELEASE DATE: October 18, 2002
PA NUMBER: PA-03-012

Letter of Intent: December 20, 2002; December 20, 2003; December 20, 2004
Application Deadline: January 24, 2003; January 23, 2004; January 24, 2005
EXPIRATION DATE: September 27, 2005, unless reissued.

Fogarty International Center (FIC) (http://www.nih.gov/fic)
National Institute of Allergy and Infectious Diseases (NIAID) (http://www.niaid.nih.gov/default.htm)
National Institute of Dental and Craniofacial Research (NIDCR) (http://www.nidcr.nih.gov/)
Centers for Disease Control and Prevention (CDC) (http://www.cdc.gov)

PURPOSE OF THIS PA

The purpose of this announcement is to invite applications from eligible institutions to train or expand the capabilities of scientists and health professionals from developing countries to engage in infectious diseases research and training not related directly to HIV/AIDS. Proposals are requested for innovative, collaborative research-training programs that would contribute to the long-term goal of building sustainable research capacity in relevant infectious diseases at developing country institutions. The intent is to harness scientific knowledge and skills to enhance prevention, treatment and control of infectious diseases causing major morbidity and mortality in endemic countries.

NIH D43 international research training award mechanism ($150,000 direct costs per year for five years)
NIAID INTERNATIONAL RESEARCH IN INFECTIOUS DISEASES (IRID) R03 PROGRAM

RELEASE DATE: June 17, 2004
PA NUMBER: PAS-04-111
EXPIRATION DATE: June 2, 2007

Department of Health and Human Services (DHHS) (http://www.os.dhhs.gov/)
COMPONENT OF PARTICIPATING ORGANIZATION:
National Institute of Allergy and Infectious Diseases (NIAID) (http://www.niaid.nih.gov)

RECEIPT DATES: October 1, 2004, February 1, 2005, June 1, 2005, etc.

PURPOSE OF THIS PA

The National Institute of Allergy and Infectious Diseases (NIAID) encourages the submission of R03 applications from institutions in eligible foreign countries to conduct preliminary or pilot studies or to explore the feasibility of, and initiate the planning of, collaborative infectious diseases research among investigators and institutions in resource-constrained countries [i.e., countries with per capita gross national income (GNI) less than US $5,000 for 200]. These grants will serve to build independent research capacity by providing direct funding to investigators who do not currently have NIAID funded grant awards for research projects. The intent of these activities is to advance the development of local scientific expertise and to increase collaborative research partnerships at NIAID international sites. Data and collaborations supported by this R03 program should lead to submission of applications for independent research funding.

Collaborative projects involving investigators and institutions from international sites and the U.S. are particularly encouraged.
RESEARCH SUPPLEMENTS FOR UNDERREPRESENTED MINORITIES

Release Date: April 9, 2001
PA NUMBER: PA-01-079
National Institutes of Health

PURPOSE

This program, originally announced in 1989, was established to address the need to increase the number of underrepresented minority scientists participating in biomedical research and the health-related sciences. Therefore, NIH has continued its efforts to establish a diversified workforce by increasing the number of individuals from underrepresented racial and ethnic groups actively participating in biomedical research. In addition, in more recent years, it has become increasingly clear that there is a serious health-care disparity among minority groups in this country. The NIH recognizes the need to expand research opportunities for minority scientists to help eliminate health disparities.

In response to these concerns, the NIH continues to emphasize the use of administrative supplements to attract underrepresented minorities to the sciences and to careers in biomedical, behavioral, clinical, and social science research. This program announcement has been endorsed by all the awarding components of the NIH and is designed to provide support for research experiences for minorities throughout the continuum from high school to the faculty level.

The NIH hereby notifies all Principal Investigators holding NIH research grants (R01, R03, R10, R15, R18, R21, R22, R24, R35, R37, P01, P20, P30, P40, P41, P50, P51, P60, U01, U10, U19, U41, U42 or U54) that funds are available for administrative supplements to existing grants for the support and recruitment of underrepresented minority investigators and students. The aim of these supplements is to attract and encourage minority individuals to enter and pursue health-related research careers in areas within the mission areas of all the awarding components of the NIH.
CHALLENGE GRANTS: BIODEFENSE PRODUCT DEVELOPMENT

RELEASE DATE: June 15, 2004
RFA Number: RFA-AI-04-029
EXPIRATION DATE: January 19, 2005

Department of Health and Human Services (DHHS)
COMPONENT OF PARTICIPATING ORGANIZATION:
National Institute of Allergy and Infectious Diseases (NIAID) (http://www.niaid.nih.gov)

LETTER OF INTENT RECEIPT DATE: December 17, 2004
APPLICATION RECEIPT DATE: January 18, 2005

PURPOSE OF THIS RFA

In response to growing concerns about the use of biological agents in acts of terrorism, the further clinical development of new vaccines, therapeutics, adjuvants, and diagnostics against NIAID Category A, B, and C priority pathogens is a high priority. This program will support further development of previously identified products against NIAID Category A, B, and C high-priority pathogens, including vaccines, adjuvants, therapeutics, and diagnostics. To be responsive to this program for the development of biodefense products, the applicant must have already demonstrated proof-of-principle for a candidate vaccine, therapeutic, adjuvant, or diagnostic method for biodefense. Phases of further development eligible for support include, but are not limited to: early validation; pre-clinical stages; scale-up; production; and fulfilling regulatory requirements.

NOTE: While clinical development strategies may be included within an overall development plan, this RFA will NOT support clinical trials. Utilization of human-derived material in pre-clinical studies in support of complying with regulatory requirements is considered responsive.
Past History of Dengue Fever in Hawai‘i

Epidemics recorded in 1852, 1856, and 1903.

A major dengue epidemic occurred in 1943-1944. In September 1943, the sampled Aedes mosquito population in Honolulu consisted of 32% *aegypti* and 68% *albopictus*.

A total of 24 confirmed cases of imported dengue virus infection were documented between 1992 and 2000 (mean cases per year, 2; range, 0-8)
Overall Organizational Structure of the Joint Collaboration Project

Vietnam PDVI Site for Dengue Surveillance and Vaccine Trials
R. Yanagihara, Director
T.T.K. Nguyen, Co-Director

University of Hawaii PDVI Team
F.D. Miller, A.R. Katz, S. Arai,
J.T. Efird, C.B. Cropp, J.H.-Tonry,
S. Togashi

Pasteur Institute PDVI Team
H.T.Q. Vu, Q.C. Luong, S.H. Le,
H.T. Diep, L.T.K. Huynh

Bien Hoa City Study Site
D.N. Tran, K.T. Nguyen, H.N. Nguyen,
H.T. Nguyen, T.V. Pham, H.H. Tran
West Nile Virus: An Impending Microbial Threat

Indicates human disease case(s).
Avian, animal, or mosquito infections.

WNV activity in 2003
Endangered Hawaiian Birds
Extinct Hawaiian Birds

Mamo

Hookbill

Kauai O'o
Detection of WNV and mosquito 18S rRNA

A primer pair (18S417/920c) was designed that allowed the detection of a 504-bp sequence of 18S rRNA in 15 different mosquito species, listed below.

<table>
<thead>
<tr>
<th>Culex nigripalpus</th>
<th>Anopheles crucians</th>
<th>Ochlerotatus taeniorhynchus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Culex restuans</td>
<td>Anopheles punctipennis</td>
<td>Ochlerotatus infirmatus</td>
</tr>
<tr>
<td>Culex salinarius</td>
<td>Anopheles quadrimaculatus</td>
<td>Mansonia titillans</td>
</tr>
<tr>
<td>Culex quinquefasciatus</td>
<td>Aedes vexans nocturnus</td>
<td>Coquillettidia perturbans</td>
</tr>
<tr>
<td>Uranotaenia sapphirina</td>
<td>Aedes albopictus</td>
<td>Toxorhynchites alboinensis</td>
</tr>
</tbody>
</table>

To date, a total of 64 mosquito pools collected on O‘ahu have been screened using this assay system. All mosquito pools were negative for a 312-bp sequence of the WNV nonstructural protein-5 (NS5) gene, but positive for the 18S rRNA gene.
Epidemiology of Leptospirosis in Hawaiʻi, 1974-1998
Annual incidence rates of leptospirosis,
State of Hawaii, 1974-1998

Mean annual incidence of leptospirosis = 2.76 per 100,000, compared to national mean annual incidence rate = 0.03 per 100,000. Hawaii led the nation in reported incidence rates from 1974 until 1995, when national reporting ceased.
Confirmed leptospirosis cases, State of Hawaii, 1974-1998

Hanalei
KAUAI
100 cases
7.9/100,000

NIIHAU
1 case Waimea

OAHU
67 cases
0.3/100,000

MOLOKAI
1 case

UAHAI
5 cases
0.2/100,000

Hawaii
176 cases
5.9/100,000

Number of cases
- 0
- 1
- 2 - 4
- 5 - 14
- 15 - 24
- 25 - 40

National mean annual incidence rate = 0.03 per 100,000
Murine Typhus Cases, 1982-2001

- 1982-2001 Typhus Cases
  - Islands

Murine Typhus Cases, 2002

- 2002 Typhus Cases
  - Islands

Total cases = 89

Total cases = 47

Kahului
Kihei
Maui

1995-91 Typhus cases
Maui Park

2002 Typhus cases

Kahului
Kihei
Maui
Murine Typhus by Island, 2002: 47 Cases

Murine Typhus on Maui, 2002

Murine Typhus Cases in State of Hawaii, 2002 and 2003

Month of Illness Onset

35 cases in 2002
Strategic Plan for a Joint Clinical Research Center (JCRC) at Phramongkutklao Royal Thai Army Hospital (PMK)

Vision

The JCRC at PMK will be a full service clinical research center conducting Phase I and II human clinical trials at PMK Hospital.

Mission Statement

The central purpose of the JCRC will be to conduct start-to-finish human Phase I and II clinical trials under the strictest and highest standards of clinical research. As a collaborative initiative between the Armed Forces Research Institute of Medical Sciences (AFRIMS) and PMK in Bangkok, Thailand, the JCRC is a collaborative venture with strategic partners including the Royal Thai Army (RTA) and the University of Hawaii (UH).

Corporate Values

- The JCRC will operate in accordance with the highest standards of clinical research with the safety of the patients being the highest priority
- All research done at the JCRC will be of the highest scientific quality
- The JCRC is organizationally distinct from AFRIMS and PMK
- Funding will primarily be derived from grants to conduct clinical trials
- Supplemental funding for infrastructure will be required from government agencies, foundations, and private industry

Background and Rational

PMK and AFRIMS being co-located in Bangkok offer a unique opportunity to conduct quality clinical trials research in Asia. PMK offers access to a large potential volunteer population as the largest military hospital and referral center in Southeast Asia seeing approximately two million outpatients annually. The laboratory and research capabilities at AFRIMS and PMK provide cutting edge technology in support of the JCRC. Currently, clinical trials research in Bangkok is limited to a very few organizations with high overhead and emotional costs. A partnership between these institutions allows each other to augment the strengths of each other achieving more robust research results.

The University of Hawaii is a major founding partner of the JCRC. Through a current grant, they have developed Internet2 type connectivity between Hawaii and PMK. This infrastructure provides broadcast quality videoteleconferencing over IP between PMK and Hawaii for regularly scheduled conferences. This infrastructure and inexpensive connectivity will be essential for collaboration with outside organizations, as well as for data analysis with UH and its supercomputer. The UH PI on this proposal is also seeking planning and infrastructure funding for the JCRC through the Telemedicine and Advanced Technology Research Center (TATRC).

Through another effort, a UH faculty member has established a joint AFRIMS-PMK-UH lab for HIV investigations, which is helping to serve as the forerunner to the JCRC.
This has led to the development of a UH initiated clinical trial investigating the neurological complications of HIV. Another group of UH researchers is developing disease surveillance and infectious disease trials in Vietnam. The JCRC with its research and laboratory capabilities is seen as an important long-term partner in these efforts outside Thailand, with either a primary or supporting role.

**Strengths, Weaknesses, Threats & Opportunities**

This strategic plan addresses the following key strengths, weaknesses, threats and opportunities for a JCRC:

**Strengths:**
- Experience in field trials
- CAP certified laboratory infrastructure in place at AFRIMS
- Funding in place for Asia-Pacific Institute of Tropical Medicine at UH
- Ongoing AFRIMS-PMK-UH research in place
- Access to large patient population at PMK Hospital
- Bangkok major travel hub for Southeast Asian countries, allowing JCRC to serve as both local and regional center
- AFRMIS-PMK with convenient location near SkyTrain and bus stops
- JCRC located next to PMK Hospital for emergency situations and back-up
- Access to tropical diseases seen at prevalence rates higher than in the U.S. in order to support clinical research

**Weaknesses:**
- Need for cash influx to fully develop the JCRC for total service capability
- Personnel need to be identified, hired, trained, and put into one organizational structure
- Lack of experience in conducting clinical trials in house
- Need to contract long term space
- Need to establish funding mechanism to pay for establishment and running of the JCRC, salaries, etc.
- Train-up time to become fully functional
- IT infrastructure needs to be purchased and put into place

**Threats:**
- Competition from Mahidol University CRC and other universities and hospitals
- Inertia among bureaucratic organizations

**Opportunities:**
- Growing need for clinical trials in Asia
- Increased funding from outside sources such as NIH for infectious disease research and BT research
- Motivated partners seeking opportunities to expand research
Business Objectives

- Provide the partner institutions and researchers with a location to perform high quality clinical trials with full service support to include QA/QC, IT, and administration.
- To become the leading, innovative clinical trials research center in Asia
- Attract more partners to include the pharmaceutical industry and other academic institutions

Key Strategies

- Secure space in the new PMK outpatient family practice building to build the JCRC
- Secure funding through partners and investors such as NIH, WRAIR, and USAMRMC
- Identify key positions required to develop and run the JCRC
- Identify and hire, if necessary, key personnel to fill the positions
- Build the infrastructure to support the JCRC to include QA/QC programs, IT systems, training programs, administration, and documentation.
- Establish track record with clinical trials already developed and waiting for implementation
- Market capabilities using successes to attract new partners to include pharmaceutical and academic partners

Major Goals

- Have JCRC space identified and contract signed and in place by May 2004
- Have JCRC Director named by June 2004
- Have JCRC key personnel identified and/or hired by 1 Sep 04
- Have JCRC staff trained by 1 Oct 04
- Have SOPs and regulatory affairs documents in place by 1 Oct 04
- Have JCRC IT infrastructure in place by 1 Sep 04
- Initiate first clinical trial NLT 1 Nov 04
Principal Investigator/Program Director (Last, first, middle):

**BIOGRAPHICAL SKETCH**

Provide the following information for the key personnel in the order listed for Form Page 2. Follow the sample format for each person. DO NOT EXCEED FOUR PAGES.

<table>
<thead>
<tr>
<th>NAME</th>
<th>POSITION TITLE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lawrence P.A. Burgess, MD</td>
<td>Associate Dean Government Affairs, Director of Telemedicine, Professor of Surgery</td>
</tr>
</tbody>
</table>

**EDUCATION/TRAINING** (Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)

<table>
<thead>
<tr>
<th>INSTITUTION AND LOCATION</th>
<th>DEGREE (if applicable)</th>
<th>YEAR(s)</th>
<th>FIELD OF STUDY</th>
</tr>
</thead>
<tbody>
<tr>
<td>U.S. Military Academy, West Point, NY</td>
<td>B.S.</td>
<td>1972-1976</td>
<td>Chemistry</td>
</tr>
<tr>
<td>John A. Burns School of Medicine, Univ. of Hawaii, Honolulu, HI</td>
<td>M.D.</td>
<td>1976-1980</td>
<td>Medicine</td>
</tr>
<tr>
<td>Tripler Army Medical Center, Honolulu, HI</td>
<td>Internship</td>
<td>1980-1981</td>
<td>Flexible</td>
</tr>
<tr>
<td>Tripler Army Medical Center, Honolulu, HI</td>
<td>Residency</td>
<td>1981-1985</td>
<td>Otolaryngology</td>
</tr>
<tr>
<td>Stanford University Medical Center</td>
<td>Fellowship</td>
<td>1985-1986</td>
<td>Head and Neck Surg.</td>
</tr>
</tbody>
</table>

**A. Positions and Honor**

**Appointments and Positions**

1994-1997 Chief, Otolaryngology-Head and Neck Surgery Service and Residency Program Director, Tripler AMC, Honolulu HI
1997-2001 Chief, Dept. of Surgery, Tripler AMC, Honolulu HI
2000-2004 American Board of Otolaryngology, Senior Examiner
2002-2004 Associate Dean for Clinical Affairs, John A. Burns School of Medicine, Univ. of Hawaii
2002-2004 Dir. Telemedicine and Simulation, John A. Burns School of Medicine, Univ. of Hawaii
2002-2004 Vice President, University Clinical Education Research Associates (Faculty Practice Plan School of Medicine), Honolulu, HI
2004-2004 Associate Dean for Government Affairs, John A. Burns School of Medicine, Univ. of Hawaii

**Honors**

1989 Military Region Award Winning Paper, American College of Surgeons Committee on Trauma, Residents'Paper Competition (co-author)
1990 Ira Tresley Research Award, American Academy of Facial Plastic and Reconstructive Surgery
1990 Certificate of Honor, Amer.Acad.Otolaryngology-Head and Neck Surgery
1992 Honorable Mention, Candidate's Thesis, American Laryngological, Rhinological and Otological Society
2000 Lewis Aspey Mologne Award, Army Surgeon General's Award for Military Academic Excellence

**B. Selected Peer-Reviewed Publications** (of 51 peer reviewed articles, 1 book, 5 book chapters, 1 web site)


Principal Investigator/Program Director (Last, first, middle):


C. Research Support

1 August 2000-30 Sept 02 A Military Unique Curriculum Web Site
Tripler Army Medical Center, Principal Investigator, federal congressional funding through the Pacific Telehealth and Technology HUI, Tripler, HI. Develop and implement a distance learning web site for Army Interns nation wide.

1 July 01-30 July 04 University of Hawaii Telemedicine Curriculum Project
John A. Burns School of Medicine, Principal Investigator, federal congressional funding through TATRC, MRMC, Ft. Detrick, MD. Develop and validate a telemedicine curriculum for the DOD.

01 November 02-31 Oct 04 Thailand-Hawaii Interactive Medical Exchange Program
University of Hawaii, John A. Burns School of Medicine. Principal Investigator, Freeman Foundation Award. Project engenders medical conferences between Thailand, Hawaii, and other Asian schools fostering international exchange through high bandwidth connectivity.

1 January 02-31 Dec 05 Bioterrorism Preparedness Infectious Disease
University of Hawaii, John A. Burns School of Medicine. Principal Investigator, funding through TATRC, MRMC, Ft. Detrick, MD. A project looking at bioterrorism preparedness issues for infectious disease.
Richard Yanagihara, M.D., M.P.H.

Dr. Yanagihara is a distinguished professor at the University of Hawaii: Professor, Departments of Pediatrics, Public Health Sciences and Epidemiology, and Tropical Medicine and Medical Microbiology, John A. Burns School of Medicine; Director, Pacific Center for Emerging Infectious Diseases Research; Director, RCMI Program; Co-Director, Pacific Research Center for Marine Biomedicine; University of Hawaii at Manoa, Honolulu.

He received fellowship training in infectious diseases at the University of Colorado Health Sciences Center (Dr. Kenneth McIntosh) and post-doctoral training in virology at the National Institutes of Health (Dr. Carleton Gajdusek). Although board certified in pediatrics, his career path has been that of a biomedical researcher. Dr. Yanagihara has long been investigating factors which contribute to the emergence or re-emergence of infectious diseases. These scientific explorations have taken the form of problem-based, disease-oriented, long-term, high-risk, multidisciplinary, opportunistic investigations of medically urgent phenomena of worldwide relevance, conducted largely in the context of exploiting naturally occurring paradigms of high-incidence 'place diseases' among populations isolated by virtue of genetics, culture and/or geography. His scholarly contributions are impressive, consisting of nearly 200 peer-reviewed articles published in high-impact journals. Notable among his landmark achievements have been the discovery and characterization of genetically distinct variants of human T-cell lymphotropic virus type I (HTLV-I) in remote Melanesian populations in Papua New Guinea and Solomon Islands, and the clarification of the worldwide epizootiology and molecular phylogeny of hantaviruses, including the highly lethal sigmodontine rodent-borne hantaviruses which cause a terrifying, frequently fatal respiratory disease, now known as hantavirus pulmonary syndrome (HPS).
Dr. Greg T. Mogel, MD

Dr. Greg T. Mogel, MD, is Assistant Professor of Radiology at the Keck School of Medicine, University of Southern California in Los Angeles, CA. Additionally he holds an appointment as Adjunct Professor at the John A. Burns School of Medicine, University of Hawaii. Prior to his academic career, Dr. Mogel spent 10 years as an active duty officer in the US Army Medical Corps. Dr. Mogel was instrumental in the establishment of the Telemedicine and Advanced Technology Research Center (TATRC) and served as the Deputy Director, managing over $100M in advanced medical technology research for the US Department of Defense. As a civilian he continues to serve as Special Assistant to the Director of TATRC. Dr. Mogel remains active in a wide variety of medical research programs ranging from digital imaging to medical robotics. Dr. Mogel, a Diplomate of the American Board of Radiology, received his medical training at the University of Pennsylvania after graduating Summa Cum Laude from Temple University in Philadelphia, PA. He remains clinically active and his research interests are related to the impact of advanced technology on the practice of medicine and the development of novel applications of medical imaging in the clinical setting by exploiting new forms of networking, decision support and informatics.
Duane J. Gubler, ScD

Duane J. Gubler, ScD, is the newly named Director, Asia Pacific Institute of Tropical Medicine and Infectious Diseases, University of Hawaii, John A. Burns School of Medicine. He recently completed a distinguished career with the Centers for Disease Control (CDC) and Prevention, where he was Division Director of Vector Borne Infectious Diseases, National Center for Infectious Diseases. He is internationally renowned for his research in Dengue Hemorrhagic Fever, and serves on the WHO Technical Advisory Committee and the Global Strategy Steering Committee for Dengue Hemorrhagic Fever. He has also served as a consultant for numerous national and international health agencies including WHO, PAHO, NIH, DoD, IDRC, and USAID. His knowledge of establishing laboratory networks for the isolation and identification of infectious diseases including agents of bioterrorism will be essential in developing the data analysis algorithms to analyze such data and provide decision support tools for outbreak surveillance, detection, and management.
COL Suwicha Chitpatima, PhD

COL Chitpatima is the Director of International Affairs for the Royal Thai Army Medical Department (RTAMD). He received his post-graduate degree in molecular biology from Tufts University. He has worked closely with Dr. Burgess on the THAI-HI project, a combined University of Hawaii and RTAMD research grant, and has been instrumental in fostering a growing relationship with the University of Hawaii (UH). He also is collaborating with UH professors Gerome Kim and Cecilia Shakuma on a clinical trial in neurocomplications of HIV. This will be the first study for the newly formed Joint Clinical Research Center (JCRC). The Surgeon General of the RTAMD, LTG Pravit Tanprasert, MD, recently named COL Chitpatima the Director of the JCRC. COL Prinya Thavichaigarn was named the Clinical Director.
Robert Teoh

Robert Teoh, MSBS MD FRCP, VP clinical operations, PPD Asia, was founder and managing director of ProPharma, a pan-Asian clinical research organization which he sold to PPD Inc in 2002. His prior industry experience was in Tanox Inc, USA, Quintiles in East Asia, and Sandoz Pharma (now Novartis) in East Asia and Switzerland. Robert served on the board of the Institute of Molecular & Cell Biology, the premier biomedical research institute in Singapore, and on advisory committees of the Economic Development and National Science & Technology Boards of the Singapore government. He qualified in medicine (1971) from the University of Newcastle upon Tyne, England and trained in clinical neurology in London at the National Hospital for Nervous Diseases, Hammersmith Hospital, and Guys Hospital. Following a MRC research fellowship, he held faculty positions at Johns Hopkins University and the Chinese University of Hong Kong.
May 27, 2004

Lawrence Burgess, M.D.
Director of Government Affairs and Director of Telemedicine
University of Hawaii – John A. Burns School of Medicine
222 S. Vineyard Street #602
Honolulu, HI 96813

SUBJECT: Establishment of a Joint Clinical Research Center (JCRC) in Infectious Disease between PMK-UH-AFRIMS
REF: Your letter of April 29, 2004

Dear Dr. Burgess,

Thank you for your letter and your interest in our continuous collaboration. It has been the Royal Thai Army Medical Department vision to form tangible and fruitful collaboration on international scale. I am pleased to hear that yet another partnership has been established and hope that we can help you in making this endeavor matriculate into another highly successful and sustainable collaboration.

In reply to your letter referenced above, as the Surgeon General of the Royal Thai Army Medical Department, I hereby authorize the following officers to participate in the newly established JCRC:

1. Senior COL Suwicha Chitpatima as The Director of the Center.
2. Senior COL Pariya Thavichaigarn as The Clinical Director of the Center.

In addition, I would be honored to co-host the planning conference here in Bangkok June 16-18, 2004. If there is anything I can do in my official and personal capacity to be of further assistance, please do not hesitate to contact me at the earliest convenience.

Sincerely,

[Signature]

LTG Pravit Tanprasert, M.D., F.A.C.C.
The Surgeon General
Bioterrorism Preparedness:
Clinical Trials Center in Infectious Disease
June 15-18, 2004
Bangkok, Thailand
Telehealth Research Institute (TRI)
University of Hawaii, John A. Burns School of Medicine
In collaboration with:
Armed Forces Research Institute of Medical Sciences (AFRIMS)
Royal Thai Army Medical Department

The University of Hawaii Telehealth Research Institute will hold a Bioterrorism Preparedness Conference on **15-18 June 2004** in **Bangkok, Thailand**. The purpose of this meeting is to: 1) further define the problem of Clinical Trials Research for Bioterrorism Preparedness, 2) discuss laboratory capabilities in Southeast Asia which are integral to such a partnership, while providing important infrastructure for related disease surveillance and outbreak management, 3) further define the partnership between UH-PMK-AFRIMS, 4) explore other organizations that could partner with this consortium, and 5) identify potential funding sources for such a Center.

Please note that limited funding is available from our grant. Participants will need to provide for their own transportation and lodging costs. If traveling from outside of Asia, it is highly recommended that you arrive on Monday, June 14th, as most flights arriving on the 15th arrive late in the evening, and we begin early on the 16th. **Please RSVP by 7 May (and e-mail or fax attached application form).** You will be responsible for your own travel arrangements.

A block of rooms has been reserved at the Four Seasons Hotel at government rates, with breakfast included. We will make initial reservations for you at the hotel. Once you receive your confirmation, you will be responsible to provide the hotel with your credit card information for late arrival or to make any changes in your arrival or departure dates. **Please reply by 7 May or the rooms will be released.** After that time, the contracted rate may or may not be available.

We look forward to seeing you soon in Thailand!

Lawrence Burgess, MD
Course Director
Dir., Institute of Telehealth and Medical Simulation
University of Hawaii, John A. Burns School of Medicine
CONFERENCE OVERVIEW

In an era of dramatically increased travel, rapid natural (and even engineered) manipulation of infectious agents, as well as security concerns related to bioterrorism, a new means of testing and evaluation for vaccine and antibiotic therapy is desperately needed. While both the DOD and NIH have been long focused on this problem, there remains significant difficulty in providing timely research when the majority of affected populations for these diseases live on foreign soil. To address this problem, the ideal scenario would consist of a foreign-based Clinical Trials center fully integrated with the most advanced technologies in broadband medical networking and clinical informatics assuring local and regional access to affected patient populations and seamless integration with state of the art US research methods.

Beyond technology, new models of integrating government agencies, non-governmental organizations and private industry could be tested in such a setting. A US certified laboratory with a large animal lab including primates would be a necessity to support such a clinical trials unit, as well as a close working relationship with a friendly host nation’s medical personal. The Center should also have a major affiliation with one or several US universities conducting both basic science and clinical research at the Center. The Center should also have broadband links to the US for transfer of data, and collaboration with ongoing genomics and proteomics researchers in the field.

Through existing grants and relationships, a partnership to address this problem is emerging between the University of Hawaii (UH), Phramongkutklao (PMK) Medical Center, and the Armed Forces Research Institute of Medical Science (AFRIMS). These two organizations share the same campus in Bangkok, Thailand. Other partnerships in the region are also possible for UH through this association.

The objectives of this meeting are to: 1) further define the problem, 2) discuss laboratory capabilities in the region which are integral to such a partnership, while providing important infrastructure for related disease surveillance and outbreak management, 3) further define the partnership between UH-PMK-AFRIMS, 4) explore other organizations that could partner with this consortium, and 5) identify potential funding sources for such a Center.
APPLICATION FORM:

Name: ____________________________
Preferred Name for Name Tag: ____________________________
Affiliation: ____________________________
Address: ____________________________
City: ____________, State: ____________, Zip Code: ____________
Telephone: ____________, Fax #: ____________
Preferred E-mail Address: ____________________________
Date of Arrival: ____________ Date of Departure: ____________
Circle Room Preference smoking non-smoking
# of Guests _______________________ Ages if <18 _______________________
Flight Arrival time: _______________________ Airlines _______________________
Flight Departure time: _______________________ Airlines _______________________
Other requests, limousines from airport:

Please e-mail or fax this application form to:
Dolly Puchert, UH Telemedicine Project Office
Fax: 808-521-8646; e-mail: dollyp@hawaii.rr.com
## Agenda

**BioTerrorism Preparedness: Clinical Trials in Infectious Disease**  
Bangkok, Thailand  
June 15 -18, 2004

### Day 1 – Tuesday, June 15, 2004

<table>
<thead>
<tr>
<th>Location</th>
<th>Time</th>
<th>Topic</th>
<th>Presenter</th>
</tr>
</thead>
<tbody>
<tr>
<td>Four Seasons,</td>
<td>1300-1500</td>
<td>Program review: Final coordination with RTA,</td>
<td>Program Committee</td>
</tr>
<tr>
<td>Montathip II Board Room</td>
<td></td>
<td>AFRIMS, hotel staff, schedule modification</td>
<td></td>
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<tr>
<td>Four Seasons</td>
<td>1500 - 1800</td>
<td>Registration; Speaker Ready Room Open</td>
<td>All Participants; Speakers</td>
</tr>
<tr>
<td>Four Seasons,</td>
<td>1800 - 1930</td>
<td>Welcome Reception! Networking, group</td>
<td>All Participants</td>
</tr>
<tr>
<td>Lobby, Private Table</td>
<td></td>
<td>discussions.</td>
<td></td>
</tr>
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</table>

### Day 2 – Wednesday, June 16, 2004

<table>
<thead>
<tr>
<th>Location</th>
<th>Time</th>
<th>Topic</th>
<th>Presenter</th>
</tr>
</thead>
<tbody>
<tr>
<td>Four Seasons,</td>
<td>Breakfast</td>
<td>Breakfast on own</td>
<td>All Participants</td>
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<tr>
<td>Blscotti</td>
<td>served until 1030</td>
<td>Planning for 2005 conference</td>
<td>Program Committee</td>
</tr>
<tr>
<td>Four Seasons,</td>
<td>0900-1100</td>
<td>Speaker Ready Room Open</td>
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<tr>
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<td></td>
<td></td>
</tr>
<tr>
<td>Four Seasons,</td>
<td>1100 - 1130</td>
<td>Registration</td>
<td>Lawrence Burgess, M.D.</td>
</tr>
<tr>
<td>Montathip II Boardroom, Lobby level</td>
<td></td>
<td></td>
<td>University of Hawaii, Jonn A. Burns School of Medicine (JABSOM)</td>
</tr>
<tr>
<td>Four Seasons,</td>
<td>1130 - 1200</td>
<td>Luncheon Meeting: Welcome, Administrative</td>
<td>COL Carl Mason</td>
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<tr>
<td>Montathip II Boardroom, Lobby level</td>
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<td>Announcements, Conference Overview</td>
<td>Commander, Armed Forces Research</td>
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<tr>
<td>Four Seasons</td>
<td>1200 - 1250</td>
<td>Dengue Fever: Update 2004</td>
<td>COL Suwicha Tim Chitpatima</td>
</tr>
<tr>
<td>Four Seasons</td>
<td>1250 - 1300</td>
<td>Break</td>
<td>Royal Thai Army Medical Department</td>
</tr>
<tr>
<td>Meet in Lobby, Four</td>
<td>1300 - 1330</td>
<td>Travel to Phramongkutklao (PMK) Medical</td>
<td>Duane Gubler, ScD</td>
</tr>
<tr>
<td></td>
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<td>Center</td>
<td>Director, Asia-Pacific Institute of Tropical Medicine and Infectious Diseases, Univ. of Hawaii University of Hawaii, Jonn A. Burns School of Medicine</td>
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<tr>
<td></td>
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<td>All Participants</td>
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<tr>
<td>Time</td>
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<tr>
<td>1330 - 1600</td>
<td>Welcome to PMK, Tour of facilities - Presentations of ongoing UH-PMK collaborations (THAI-HI project, Trial in Neurological Complications of Infectious Disease, Bioterrorism Preparedness-Clinical Trials Center)</td>
<td>PMK Medical Center</td>
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<tr>
<td>1600 - 1630</td>
<td>Travel to Four Seasons</td>
<td>Four Seasons</td>
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<tr>
<td>1630 - 1830</td>
<td>Informal discussions, free time</td>
<td>Four Seasons</td>
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<tr>
<td>1830 - 2130</td>
<td>Networking reception, THAI Set dinner meeting: Introduction of THAI, US, Hawaii guests of honor</td>
<td>Seasons, Montathip II Conference Room, Lobby level</td>
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**COL Suwicha Tim Chitpatima**  
Royal Thai Army Medical Department
### Day 3 – Thursday, June 17, 2004

<table>
<thead>
<tr>
<th>Location</th>
<th>Time</th>
<th>Topic</th>
<th>Presenter</th>
</tr>
</thead>
<tbody>
<tr>
<td>Four Seasons, Biscotti</td>
<td>0630 - 0800</td>
<td>Breakfast on own; Informal discussions, Conference Room Open</td>
<td>All Participants</td>
</tr>
<tr>
<td>Meet in Lobby, Four Seasons AFRIMS</td>
<td>0800 - 0830</td>
<td>Travel to AFRIMS</td>
<td>All Participants</td>
</tr>
<tr>
<td>AFRIMS</td>
<td>0830 - 1130</td>
<td>Introduction to AFRIMS, Tour of facilities including Animal Laboratories</td>
<td>COL Carl Mason, Commander, AFRIMS</td>
</tr>
<tr>
<td>In transit</td>
<td>1130 - 1200</td>
<td>Travel to Bumrungrad Hospital</td>
<td>All Participants</td>
</tr>
<tr>
<td>Bumrungrad Hospital</td>
<td>1200 - 1500</td>
<td>Introduction to Bumrungrad Hospital; Tour of facilities, Clinical Trials Center</td>
<td>All Participants</td>
</tr>
<tr>
<td>In transit</td>
<td>1500 - 1530</td>
<td>Travel to Four Seasons</td>
<td>All Participants</td>
</tr>
<tr>
<td>Four Seasons</td>
<td>1530 - 1830</td>
<td>Informal discussions, free time</td>
<td>All Participants</td>
</tr>
<tr>
<td>Four Seasons, Madison, Lobby level, off of courtyard</td>
<td>1830 - 2130</td>
<td>Planning dinner meeting: 2004 Conference discussion, plans for 2005; Speakers suggestions for JCRC</td>
<td>Speakers, Program Committee</td>
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### Day 4 – Friday, June 18, 2004

<table>
<thead>
<tr>
<th>Location</th>
<th>Time</th>
<th>Topic</th>
<th>Presenter</th>
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</thead>
<tbody>
<tr>
<td>Four Seasons, Montathip II Boardroom, Lobby level</td>
<td>0745 - 0900</td>
<td>Breakfast Meeting: University of Hawaii and Research in Infectious Diseases</td>
<td>Duane Gubler, ScD, Director, Asia-Pacific Institute of Tropical Medicine and Infectious Diseases, Univ. of Hawaii, Rick Yanagihara, MD, MPH, Dept. of Pediatrics, Univ. of Hawaii</td>
</tr>
<tr>
<td>Montathip II Boardroom</td>
<td>0900 - 1000</td>
<td>Industry Sponsored Clinical Trials in Asia</td>
<td>Robert Teoh, MSBS MD FRCP, VP Clinical Operations, Asia-PDD, All Participants</td>
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<tr>
<td>Montathip II Boardroom</td>
<td>1000 - 1015</td>
<td>Break</td>
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<tr>
<td>Montathip II Boardroom</td>
<td>1015 - 1245</td>
<td>UH-AFRIMS-PMK Clinical trials, alone or in collaboration with others: problem definition, constructing relationships, funding possibilities</td>
<td>Lawrence Burgess, M.D., University of Hawaii, John A. Burns School of Medicine (JABSOM) Gregory Mogel, M.D., TATRC, USAMRMC, Ft. Detrick, MD, COL Carl Mason</td>
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<tr>
<td>Montathip II Boardroom</td>
<td>1245 -1300</td>
<td>Concluding Remarks</td>
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<tr>
<td>Time</td>
<td>Event</td>
<td>Location</td>
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<tr>
<td>1300</td>
<td>Adjourn</td>
<td>Four Seasons</td>
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<tr>
<td>1300-1600</td>
<td>Conference Analysis, Wrap-up</td>
<td>Montathip II Boardroom</td>
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Program Committee