# Faculty of Tropical Medicine
# Mahidol University

# Annual Review 2005

# Contents






**Faculty of Tropical Medicine Mahidol University, Annual Review 2005**

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ISSN 1686-381X

# Foreword
## from the Dean

In my first year as Dean of the Faculty of Tropical Medicine, Mahidol University, it is indeed my honor to present the Faculty's Annual Review 2005. The term of Prof. Sornchai Looareesuwan as Dean of the Faculty of Tropical Medicine ended on 30 September 2004, with myself, Assoc. Prof. Pratap Singhasivanon, succeeding in this position for the ensuing 4 years. Prof. Sornchai achieved many things during his terms as Dean, and my colleagues and I aim to strengthen the Faculty further as "Asia's Leader in Tropical Medicine", through research, education, and services.

### Summary of activities

**Research**

The Faculty of Tropical Medicine encourages basic and applied research that leads to the solution of clinical problems in the tropics, and to improving the quality of life of the people, particularly those in tropical and developing countries. Research activities are focused on the development of new knowledge or innovations for the practice of tropical medicine. There are several related organizations within the Faculty to facilitate, improve, and maintain research quality e.g. ethics committees, board of research consultants, and the Research and Academic Affairs Unit. We encourage collaborative studies through both local and international linkages. The Faculty is currently affiliated with more than twenty leading research institutes from all continents of the globe. As part of our research activities, we provide international postgraduate education and training in tropical medicine for scientists, physicians and others from all nations. The current research programs include clinical trials in the Bangkok Hospital for Tropical Diseases, laboratory research, field and epidemiology studies covering more than 20 diseases (including malaria, melioidosis, soil-transmitted diseases, and mosquito-borne diseases), HIV/AIDS, and the health effects of unpredicted natural hazards and disasters.

In the reporting period, members of the Faculty conducted 85 ongoing research projects, and instigated 19 new ones. One hundred and fifteen papers were published in international journals and 16 in national journals. Seventy-nine papers were presented at international conferences and 7 at national conferences. The Faculty remains the leader in Asia in publishing research studies on malaria and other tropical diseases. We will continue to encourage, support, and facilitate research in tropical disease and other related global health problems. The research activities of the Faculty of Tropical Medicine will continue to strive to improve the education and health of the people in this region.

**Education**

The Bangkok School of Tropical Medicine offers six regular international postgraduate programs-the Diploma in Tropical Medicine and Hygiene, Master of Clinical Tropical Medicine, Master of Clinical Tropical Pediatrics, Master of Science in Tropical Medicine, Doctor of Philosophy in Tropical Medicine, and Doctor of Philosophy in Clinical Tropical Medicine. In the year 2004, we enrolled 32 new DTM&H students from 17 countries, 29 MSc students from 4 countries, and 18 PhD students from 2 countries. In total, 235 students were enrolled in the six programs (DTM&H: 32; MCTM: 5; MCTP: 2; MSc: 79; and PhD: 117, while 75 students graduated. To date, participants from more than 50 different countries have attended the Faculty's international programs.

### Joint International Tropical Medicine Meeting 2004

In 2004, the annual Joint International Tropical Medicine Meeting (JITMM 2004) was co-organized with the Parasitology and Tropical Medicine Association of Thailand, TROPMED Alumni Association, SEAMEO TROPMED Network, and the Asian Centre of International Parasite Control (ACIPAC). The Meeting was held from 29 November to 1 December 2004, at the Ambassador Hotel, Bangkok, and attracted 643 delegates from 25 countries, and there were 123 oral and 107 poster presentations. Dr. Robert G. Ridley, world-renowned Director of the TDR Programme for Research and Training on Tropical Diseases, presented the 10th Chamlong-Tranakchit Harinasuta Lecture, entitled "Directions for Tropical Disease Research in the Next 10 Years".

### Collaborations

The Faculty has ongoing collaborative relationships in research and training with over 30 institutions internationally. Thirteen new Memoranda of Understanding were signed with international institutions, and four with national institutions.

### Finance

Total expenses amounted to 235.55 million Baht, of which 139.80 million Baht were supported by government budget, and 95.74 million Baht was derived from Faculty revenue.

### Personnel

In the year 2004, there were 788 staff in the Faculty, comprising 97 academic staff, 147 support staff, and 544 administrative staff. 64 staff (66%) had PhDs, while 33 staff (34%) had Master Degrees or comparable qualifications. Two staff were promoted to Associate Professor, and 4 to Assistant Professor. The ratio of Professor: Assoc. Prof. : Assist. Prof. : Lecturer = 5 : 33 : 32 : 27, respectively; 163 new staff were recruited, 94 resigned, 9 retired, and 6 took early retirement during the year.

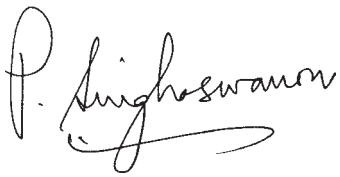
### Staff development

Six staff have been continuing their education within Thailand, and 5 overseas. Ten staff were trained within Thailand and 16 overseas. Forty-three staff participated in international conferences and 682 in national conferences.

### Construction and area development

Recent developments have included the construction of a new building on the main campus. This building includes a Global Information System (GIS) network center and a Tropical Disease Reference Center and Museum. The building will be finished at the end of 2005.

Finally, I wish to convey my sincere appreciation to all members of the Faculty, to our supporters and collaborators for their excellent work throughout the year 2004. I trust that the Faculty of Tropical Medicine Annual Review 2005 provides a comprehensive summary of the Faculty's activities in 2004, and I commend it to you.



**Pratap Singhasivanon**
Dean

# Editor's Note

**Dear Readers,**

The Annual Review 2005 is a compilation of Faculty of Tropical Medicine achievements for the calender year 2004. Besides Departmental and Unit activities, research projects and publications are listed and Abstracts of both published paper and papers presented at International and National meetings are compiled.

In this issue, Assoc. Prof. Pratap Singhasivanon, the new Dean, has reported the Faculty's activities in summary, and the details may be found inside.

I hope that this Annual Review 2005 will provide you with an insight into the Faculty of Tropical Medicine, and be pleasing for all our readers. Your opinions, suggestions, and complaints, are welcome to improve our next issue.

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Dean

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**Mr. Chanathep Pojjaroen-anant**
Deputy Dean for Environment
and Land Resource

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Assistant Dean for Research

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Assistant Dean for Educational
and Information Technology

**Mrs. Vorapan Singhsilarak**
Secretary of the Faculty

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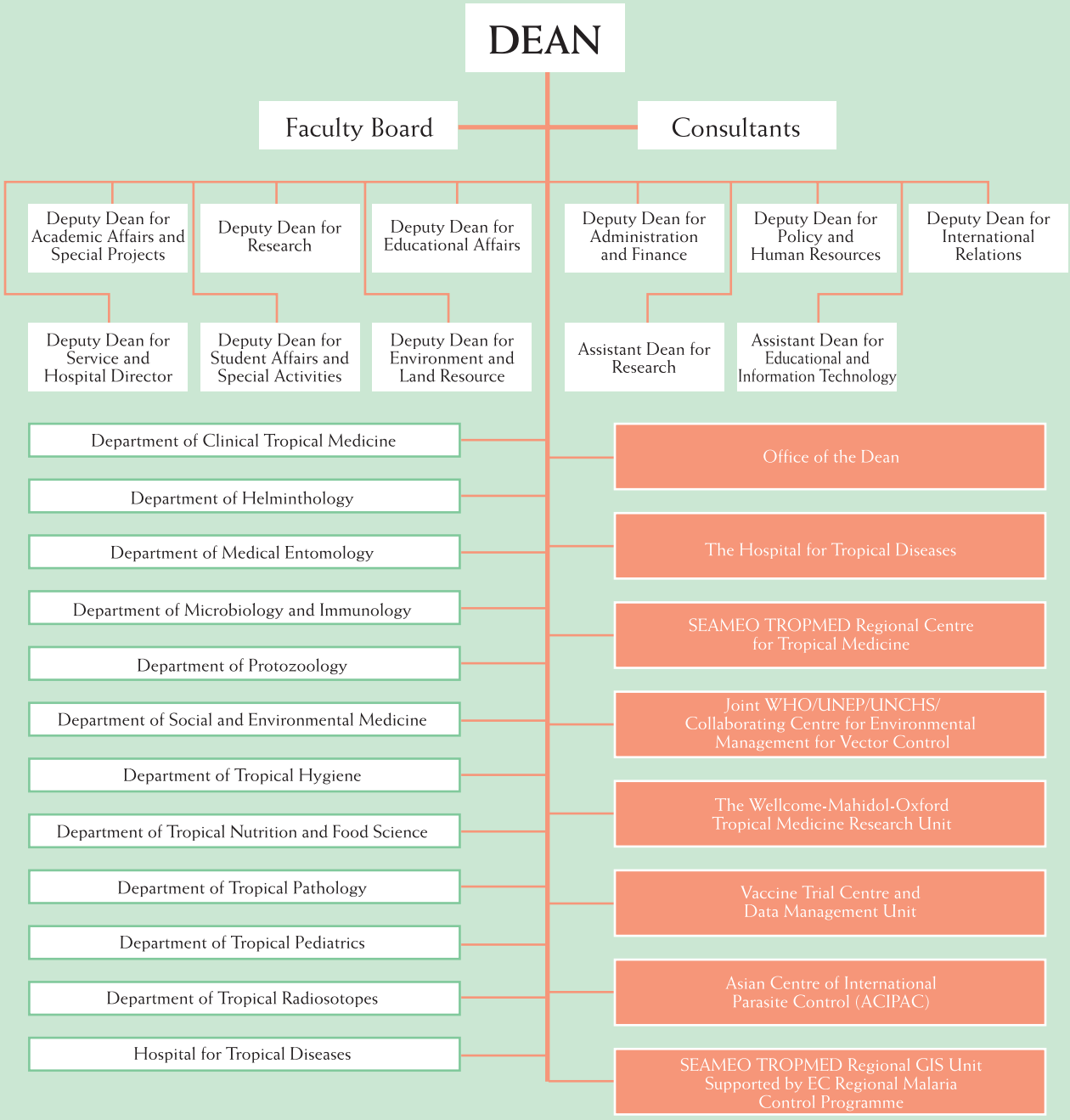
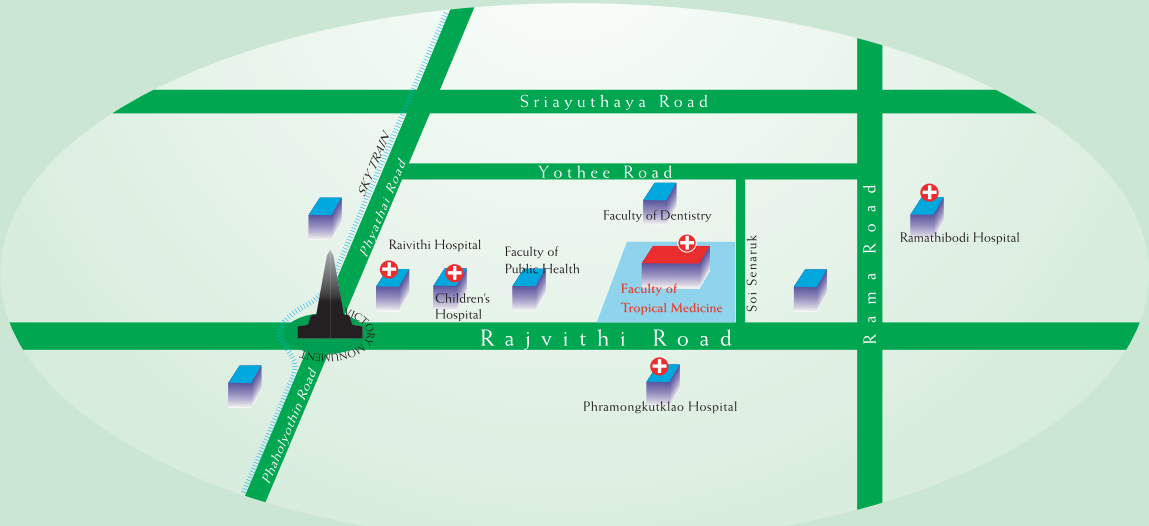
# Organization Chart




■ The Asian Centre of International Parasite Control (ACIPAC) organized the Workshop on Global Parasite Control Initiative 2004 : Future Directions for Partnership Development in Parasitic Disease Control, 27-28 March 2004, at the Siam City Hotel, Bangkok.


■ Opening ceremony of the ACIPAC International Training Course on School-based Malaria and Soil-transmitted Helminthiases Control for Programme Managers, June 2004, in the Chalermprakiat Building, Faculty of Tropical Medicine.


■ Opening ceremony of DTM&H 2004 course, April 2004 in the Chalermprakiat Building, Faculty of Tropical Medicine.


■ His Excellency Pehin Dato Haji Abdul Aziz Umar, Minister of Education, Brunei and his team visited the Faculty of Tropical Medicine, SEAMEO Council President, SEAMEO TROPMED Network and ACIPAC, in May 2004.

■ Prof. Srisin Khusmith, Vice President for Research, Mahidol University and Mrs. Rattana Pheturai, Director of Research Management Division, Mahidol University gave a special talk on "Mahidol University Research Funding" on 6 September 2004, at the Faculty of Tropical Medicine.


■ The exceutives and staff of Tropmed placed a wreath on Mahidol Day, 24 September 2004.

■ Assoc. Prof. Pratap Singhasivanon, Dean, and his management team outlined management policy to Faculty members, on 5 October 2004.

■ Graduation Day 2004.

■ Thai Traditional Medicine training for 14 overseas participants, 28 July 2004.

■ Opening Ceremony for the Collaborative Project to Produce of Rural Doctors, 27 December 2004.



■ Special Lecture "Role of Tropical Medicine in Health Development" by Dr. Samlee Plianbangchang, 2 July 2004

■ Special Talk
"Rabies and its related viruses: the global problem" by Prof. David A. Warrell 26 August, 2004, Chalermprakiat Building.



■ Joint International Tropical Medicine Meeting 2004, 29 November - 1 December 2004, Ambassador Hotel, Bangkok.


■ Layins Foundation Stone Ceremony for the new Tropical Medicine Building, on the main campus.

■ Retirement Day, 21 September 2004.

■ Happy New Year 2005.

## Consultants

1. Prof. Emeritus Chamlong Harinasuta
2. Prof. Emeritus Danai Bunnag
3. Prof. Emeritus Arunee Sabchareon
4. Prof. Emeritus Chaisin Viravan
5. Prof. Emeritus Prayong Radomyos
6. Assoc. Prof. Mario Riganti
7. Prof. Emeritus Mukda Trishnananda
8. Prof. Emeritus Sommai Wilairatana
9. Prof. Sirivan Vanijjanonta
10. Dr. Peter Echeverria
11. Dr. Stephen Wheeler King
12. Lieut. Col. Dr. George Watt

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Dr. Frederick Gay
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Prof. Akira Ito
Datuk Dr. Manikavasagam Jegathesan
Prof. Dr. Chev Kidson
Prof. Dr. Gary M. Brittenham
Dr. Stephen L. Hoffman
Prof. James Carroll
Prof. Ralf Clemens
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Prof. Gunther Wernsdorfer
Prof. Masamichi Aikawa
Prof. Somei Kojima
Prof. C.P. Ramachandran
Dr. Peter F. Beales
Prof. Dr. David Warrell
Prof. John H. Cross
Prof. Myron Max Levine
Prof. Victor R. Gordeuk
Prof. Herbert M. Gilles
Prof.Dr. Sandra Bernardo Tempongko
Prof. Tsutomu Takeuchi

## Faculty Board

| | | | |
|---|---|---|---|
| 1. | Dean | | Chair |
| 2. | 11 | Deputy Deans | Members |
| 3. | 11 | Heads of Department | Members |
| 4. | 4 | Lecturer Representatives | Members (4-year term) |
| 5. | 1 | Deputy Dean | Member and Secretary |

**Faculty Senate**

| | | |
|---|---|---|
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| 2. | Assoc. Prof. Porntip Petmitr | Vice Chair |
| 3. | Assoc. Prof. Supatra Thangrungkiat | Representative, Department of Medical Entomology |
| 4. | Assist. Prof. Kriengsak Limkittikul | Representative, Department of Tropical Pediatrics |
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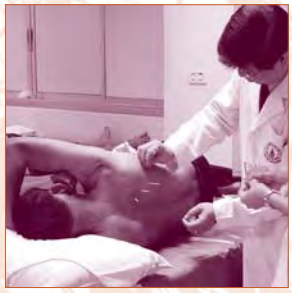
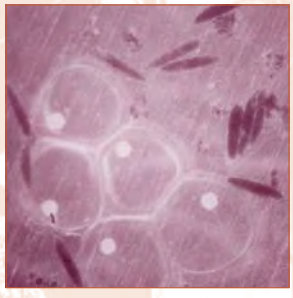
| 6. | Assist. Prof. Panyawut Hiranyachattada | Representative, Department of Helminthology |
| 7. | Miss Rachatawan Chiabchalard | Representative, Department of Protozoology |
| 8. | Assist. Prof. Talabporn Harnroongroj | Representative, Department of Tropical Nutrition and Food Science |
| 9. | Dr. Duangkamol Viroonudomphol | Representative, Department of Tropical Radioisotopes |
| 10. | Assist. Prof. Chantima Lohachit | Representative, Department of Social and Environmental Medicine |
| 11. | Assist. Prof. Apichart Nontprasert | Representative, Department of Clinical Tropical Medicine |
| 12. | Assoc. Prof. Punnee Pitisuttithum | Lecturer Representative |
| 13. | Assist. Prof. Pongrama Ramasoota | Lecturer Representative |
| 14. | Assist. Prof. Urai Chaisri | Representative, Department of Tropical Pathology/Secretary |
| 15. | Dr. Teerachai Kusolsuk | Representative, Department of Tropical Hygiene/Assistant Secretary |


# Departments and Activities

## Faculty of Tropical Medicine, Mahidol University


DEPARTMENT OF

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**ASSOC. PROF. WICHAI SUPANARANOND** Head of Department

## CURRENT RESEARCH ACTIVITIES

The Department has published more than 300 papers and has continued to pursue its mission in three major activities: teaching, research services and social welfare. The Department embarked upon clinical research on several major tropical infectious diseases.

Malaria research activities have focused on clinical trials, pathophysiology, clinical pharmacology and clinically related laboratory studies. Staff of the Department studied about 2500 admitted cases of this disease. Most of the cases were falciparum and vivax malaria and a few cases of mixed infections with malariae and ovale malaria. The major focus is on clinical trials of multidrug-resistant falciparum malaria in uncomplicated and complicated cases. Combinations of various antimalarial drugs were tested continuously; halofantrine, mefloquine, quinidine, amodiaquine, artemether and artesunate in combination with mefloquine. We found that sequential treatment with artesunate or artemether followed by mefloquine is effective, well-tolerated and suitable as an alternative treatment for multidrug-resistant malaria.

Besides extensive clinical studies, we also carried out interdepartmental and institutional collaborative studies of antigens in cerebral and non-cerebral malaria patients, of lymphocyte subpopulations during the acute and convalescence phases of malaria, and qualitative and quantitative polymerase chain reaction to predict *Plasmodium falciparum* treatment failure. Pathophysiologic alterations in malaria have been widely investigated. Interesting results were the dynamic alteration in splenic function during acute falciparum malaria, in erythrocyte survival following clearance of malaria parasites, defective production of and response to IL-2 in acute falciparum malaria, cytoadherence and ultrastructure of *Plasmodium falciparum*-infected erythrocytes from splenectomized patients and hepatic blood flow and metabolism in severe falciparum malaria.

Studies of stage specificity of quinine, chloroquine, mefloquine, artesunate, artemether and halofantrine were carried out in vivax malaria. The antimalarial efficacy of tetracycline, doxycycline, rifampicin and azithormycin was also studied.

Parasitic infestations have also been studied, such as drug trials and investigations for gnathostomiasis and local parenteral drug application, strongyloidiasis, opisthorchiasis, paragonimiasis and teniasis.

Research series are continuing, involving new applications of antifungal drugs for AIDS with fungal disease. Traditional medicines for the treatment of HIV/AIDS are also being studied.

Research into skin diseases in HIV patients has been conducted in many aspects, the epidemiology of cutaneous manisfestations in HIV patients in Thailand, fungal infections in leukoplakia patients, and superficial fungal infections in normal and HIV patients, such as PPE, dermatophytes, leukoplakia and PCP.

The titles of current departmental research activites are as follows :

1. A worldwide, phase I dose-escalating study of the safety tolerability and immunogenicity of a three-dose regimen of the MRKAd5 HIV-1 gag vaccine in healthy adults

2. Immunogenicity and safety of quadrivalent HPV (Type 6,11,16,18) L1 virus-like particle (VLP) vaccine in 16 to 23 year-old women with an immunogenicity bridge between the HPV 16 component of the quadrivalent vaccine and the monovalent HPV 16 vaccine pilot manufacturing material and a study to evaluate the efficacy of quadrivalent HPV (Types 6,11,16, and 18) L1 virus-like particle (VLP) vaccine in reducing the incidence of HPV 6-11-and 18-related CIN, and HPV16 and 18 related external genital warts, VIN and VaIN, and HPV 16 and 18-related vulvar and vaginal cancer in 16-to 23 year-old women - The FUTURE Study.

3. Safety and immunogenicity studies of WRSd1, a live attenuated *Shigella dysenteriae* type 1 vaccine candidate in Thai adults.

4. Safety, immunogenicity, and efficacy of quadrivalent HPV (Types 6, 11, 16, 18) L1 virus-like particle (VLP) vaccine in mid-adult women - The FUTURE III (Females United to Unilaterally Reduce Endo/Ecto Cervical Cancer) Study.

5. A Phase III trial of Aventis Pasteur live recombinant ALVAC-HIV (vCP1521) priming with VaxGen gp120 B/E (AIDSVAX" B/E), boosting in HIV - uninfected Thai adults.

6. A multicenter, randomized, double-blind, phase II study to evaluate the safety, tolerance and efficacy of multiple doses of SCH 56592 versus fluconazole in the treatment of oropharyngeal candidiasis (OPC) in HIV-positive patients.

7. Open-label treatment protocol for the safety and efficacy of SCH 56592 (oral suspension) in the treatment of invasive fungal infections.

8. Efficacy and tolerability of ivermectin for gnathostomiasis.

9. Effect of drug accumulation in the neurotoxicity of artemether, dosing regimens with variable drug-free intervals in a mouse model.

10. Safety and therapeutic effects of Jin Huang Chinese medicine in uncomplicated HIV-1 patients.

11. Observational probe study of *in vitro* immune response parameters to candidate HIV-1 vaccine antigens among subjects from Thailand.

12. Neoropathological toxicity of artemisinin derivatives in a mouse model.

13. Development of field methods and investigators of the molecular basis of sulfonamide resistance in *Plasmodium vivax*.

14. Novel point mutations in the dihydrofolate reductase gene of *Plasmodium vivax*: evidence for sequential seleetion by drug pressure.

15. Asexual and sexual stage antimalarial activities of artesunate and primaquine in falciparum malaria.

16. Research and development for Thai people living at Thai-Myanmar border to free from tropical diseases.

17. Research and development on drugs and diagnostic lools for diagnosis and treatment of tropical diseases in Thailand.

18. Liver megaproject Phase 1: from basic research to education science and applied technology in clinical study.



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ASSOC. PROF. WICHIT ROJEKITTIKHUN Head of Department

## CURRENT RESEARCH ACTIVITIES

### Gnathostomiasis

- A seven-year retrospective evaluation of gnathostomiasis and diagnostic specificity by immunoblot.
- Effect of ivermectin on *Gnathostoma spinigerum* morphology.
- *Gnathostoma* infection in fish caught for local consumption in Nakhon Nayok Province.
- Seasonal variation of *Gnathostoma* infection in swamp eels in Nakhon Nayok.

### Angiostrongyliasis

- Angiostrongyliasis: partially purified antigens of *Angiostrongylus cantonensis* adult worms for diagnosis using immunoblot.
- Angiostrongyliasis: potential fractionated antigens of *Angiostrongylus cantonensis* adult worms for diagnosis using ELISA and an elimination of cross-reactive components.
- *Angiostrongylus cantonensis*: s-adenosyl methionine decarboxylase.
- Experimental infection of freshwater fish in Thailand with infective stage of *Angiostrongylus*.

### Toxocariasis

- *Toxocara canis* larval antigens for serodiagnosis of human toxocarosis.
- Evaluation of excretory-secretory and partially purified antigens of adult *Toxocara canis* againt toxocariasis by ELISA and immunoblot.

### Trichinellosis

- Monoclonal antibody-based competitive ELISA and indirect ELISA for immunodiagnosis of trichinellosis.

### Cysticercosis

- Comparison of biochemical extract preparations of *Cysticercus cellulosae* by SDS-polyacrylamide gel electrophoresis and immunoblot technique.
- Differentiation of fractionated larval antigens (*Cysticercus cellulosae*) responsible for antibody of neurocysticercosis patients.

### Echinococcosis

- Analysis of fluid antigens of *Echinococcus* cyst for diagnosis.

### Opisthorchiasis

- Diagnosis of human opisthorchiasis with *Bithynia* snail antigen by ELISA.
- Studies on the efficacy of Thai traditional herbal medicines in the treatment of opisthorchiasis in hamsters.
- Research and development of an application to purify *Bithynia* snail antigen in serodiagnosis of opisthorchiasis.

### Paragonimiasis

- Comparative studies on surface ultrastructure of adult worm of *Paragonimus* sp. in Thailand.
- Studies on *Paragonimus* populations: morphology, enzymology, molecular biology and epidemiology aspects.

### Filariasis

- Study on prevalence of *Wuchereria bancrofti* infection in Kanchanaburi and Ratchaburi provinces.
- Urine ELISA for diagnosis of Bancroftian filariasis.



## Soil-transmitted helminthiasis

- Soil-transmitted helminthiasis control through school-based intervention.
- Effect of mebendazole on *Trichuris trichiura* morphology.
- Efficacy of high dose mebendazole against trichuriasis in adult patients.
- Epidemiology and treatment of strongyloidiasis with ivermectin.
- Impact on health and nutrition of deworming children and adolescent girls.

## Other parasites

- Fish-borne trematodes in Thailand.
- Research and development of the integrated project on chemotherapy and control of malaria and parasitic infections.

## LIST OF ABSTRACTS

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DEPARTMENT OF

# Medical Entomology

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## CURRENT RESEARCH ACTIVITIES

Research conducted by the staff of the Department of Medical Entomology involves both basic and applied knowledge applicable in controlling insects and arthropods that are vectors of tropical diseases, with the emphasis on mosquito-borne diseases.

Effective controls of mosquito vectors are directed at both laboratory and field trials. Control of larvae of *Aedes aegypti* in the Faculty of Tropical Medicine premises, by Abate sand granules (temephos); studies on the efficacy of insect repellents extracted from various medicinal plants; and effective measures for preventing tropical disease infections in the population living at the Thai-Myanmar border are continuously conducted.

Inter-organization projects on various aspects, such as construction of a key for identifying of *Anopheles aconitus* and the search for malaria transmission form(s), a search for effective herbal extracts for lice control, survey of malaria vectors in Sa Kaeo Province, and effective control measures for *Brugia malayi* in Narathiwat Province, are conducted.

Several research topics in the molecular level are performed, for example, DNA bank of mosquito vectors in Thailand, genetic diversity of *Anopheles barbirostris* group in Thailand for control of tropical diseases, and specificity test of primers synthesized from DNA fragments of the *Anopheles minimus* mosquito. The effects of heavy metals, lead and cadmium, on enzymes of *Culex quinquefasciatus* larvae are also studied.

Laboratory colonies of different strains of mosquito vector species (*Anopheles*, *Aedes*, *Culex*, and *Mansonia*) are continuously maintained in the insectarium for further use.

The Department of Medical Entomology also acts as a reference center on mosquito vectors in Thailand through the establishment of the Mosquito Museum Annex. Academic consultations, especially on mosquito-borne diseases and their control measures, and also services for detecting filarial parasites, identifying of mosquitoes and other medically important insects and arthropods, are regularly provided.

### Highlight Activities

"Study on the insecticidal activities of several species of Thai herbal extracts for controlling mosquito vectors. The promising oil extracts that showed mosquito repellency included as qinghao (*Artemisia annua*), "may chang" (*Litsea cubeba*), clove (*Syzygium aromaticum*), and "makaen" (*Zanthoxylum limonella*), have been formulated in to a cream or gel. The extract of "thong pun chang" (*Rhinacanthus nasutus*) provided high larvicidal activity and has been prepared as a tablet form. The development of mosquito repellent formulation of volatile oils mixture, *Artemisia annua*, is in the process of patent application."

## LIST OF ABSTRACTS

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## CURRENT RESEARCH ACTIVITIES

1. Detection of dengue viral RNA in mosquitoes (*Aedes aegypti*) by nucleic acid sequence-based amplification (NASBA) and polymerase chain reaction (PCR).
2. Immunological studies on vector-borne disease of dengue haemorrhagic fever in Thailand.
3. Molecular study of dengue virus in Thailand.
4. Diagnosis of dengue virus infection by luminescence immunoprecipitation assay.
5. Serotypes of dengue virus infection in Petchaboon, Nakhon-Srithammaraj and Srisaket provinces.
6. Development of dot-blot ELISA for diagnosis of *Shigella* spp.
7. Comparison of Salmo-Dot and PCR for the detection of *Salmonella* spp. in foods.
8. Molecular typing of leptospiral serovars based on genes of the *rfb* locus.
9. Study of the membrane protein antigen of leptospira that react with leptospirosis patients' serum.
10. An application of nested polymerase chain reaction in detecting scrub typhus DNA from clinical specimens.
11. Analyses of natural killer T (NK-T) cell subsets in patients with severe and uncomplicated falciparum malaria.
12. Indirect immunoperoxidase test for dual serodiagnosis of scrub typhus and leptospirosis.
13. Detection of *Salmonella* enterotoxin and enterotoxin in food and clinical isolates.
14. Detection of virulence factors from *Aeromonas* spp. in relation to diarrhea.
15. Antigenic recognition of *Aeromonas* antigens in mice.
16. Detection of antibody response to the 19 kDa fragment of *Plasmodium yoelli* merozoite surface protein-1 (MSP-119) following immunization using CpG oligonucleotide and montanide ISA51 as adjuvant.
17. Purification of a *Vibrio cholerae* O1 antigen by affinity chromatography using a killing active monoclonal antibody.

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The Department of Protozoology is one of eleven departments within the Faculty of Tropical Medicine, Mahidol University. It was one of the first five departments created at the foundation of the Faculty of Tropical Medicine, in 1960. Its responsibilities are teaching, training, research and service in the field of medical protozoa.

## CURRENT RESEARCH ACTIVITIES

1. Ultrastructure of acute and chronic toxoplasmosis after pyrimethamine and artesunate administration *in vivo* study.
2. Dog and cat parasitic zoonoses.
3. Canine zoonotic giardiasis in temple-related communities in Thailand.
4. Biological contamination-free Thai frozen food.
5. Molecular technique for diagnosis of toxoplasmosis and neosporosis in Thai dairy cows.
6. Molecular and immunohistochemistry studies on stage interconversion of toxoplasmosis in immunocompromised hosts.
7. Free-living amoebae contamination in natural hot spring.
8. Molecular digonosis of malaria, amoebiasis and cryptosporiosis.
9. Purification and characterization of DNA topoisomerases from *Trichomonas vaginalis*.
10. Establish double antibody ELISA method (sandwich ELISA) for detection of *G. intestinalis, E. histolytica, B. hominis* in fecal specimens.
11. Studies on ultrastructure of *Cryptosporidium* after exposure to drugs.
12. Rapid detection of *Entamoeba histolytica* antibody.

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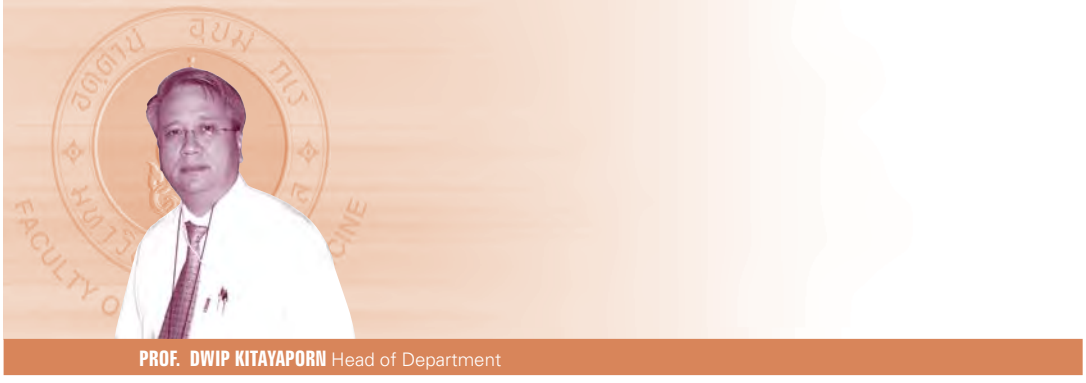

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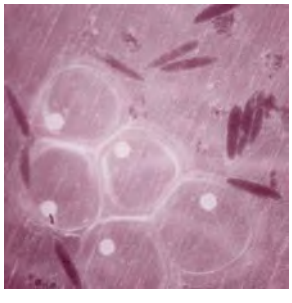
## CURRENT RESEARCH ACTIVITIES

- A phase III trial of Aventis Pasteur live recombinant ALVAC-HIV (VCP 1521) priming with VaxGen gp 120 B/E (AIDSVAX™ B/E) boosting in HIV-uninfected Thai adults.
- Integrated studies of human and animal leptospirosis in endemic areas of Nakhon Ratchasima, Thailand.
- Collaborative study to evaluate operational programme of insecticide treated bednets for malaria control in Thailand.
- Factors associated with completion and default among DOTS and self-administered therapy (SAT) for treatment of TB.
- Rapid detection of rifampicin-resistant *Mycobacterium tuberculosis* from indoor air.
- Development of a serovar-specific diagnostic test using phage antibody technique.
- Early detection of quinolone-resistant *Mycobacterium tuberculosis* from Thai TB patients.
- Epitope mapping of monoclonal antibody specific to *Burkoideria pseudomallei* using phage display technique.



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DEPARTMENT OF

# Tropical Hygiene

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The Department of Tropical Hygiene was originally named the Tropical Hygiene Section. In 1960, upon the establishment of the Faculty of Tropical Medicine, the Tropical Hygiene Section was also founded. Since then, the section has been responsible for providing lectures and field training operations as part of the Diploma of Tropical Medicine and Hygiene (D.T.M. & H.) course. Epidemiological research has also been one of the major activities of the section, responding to public health problems (i.e. scrub typhus and malaria) which afflicted the rural population during that time. In 1974, the Section was upgraded into the Department of Tropical Hygiene. At present, the department is responsible for providing instruction and training to the M.Sc. / Ph.D. degree programs in Tropical Medicine in addition to the existing D.T.M. & H. course. Most research activities being carried out at the moment are mainly epidemiological, and the application of Geographical Information System (GIS) to common tropical diseases. Furthermore, the Department has direct responsibility for managing the Rajanagarindra Tropical Disease International Center (RTIC) to ensure the continuous delivery of quality and gratuitous health services through its malaria clinic to the people within the area. The RTIC is situated in a malaria-endemic rural community near the Thai-Myanmar border in Suan Phung District, Ratchaburi Province.

## CURRENT RESEARCH ACTIVITIES

1. Epidemiology and control of malaria in Ratchaburi Province, Thailand.
2. Application of GIS in monitoring multi-drug resistant malaria in the Greater Mekong Sub-Region of Southeast Asia III.
3. Epidemiology and drug sensitivity of Enterobacteriaceae in a rural community near the Thai-Myanmar border in Suan Phung, Ratchaburi Province.
4. Study on the ecology of anopheline larvae in a malaria-endemic area.
5. Occurrence of heterophyid metacercariae Haplorchis in cyprinoid fish of 2 reserviors in Tanowsri Subdistrict, Suan Phung, Ratchaburi Province.
6. Status of intestinal helminth infections among Thai troops working along Thai-Myanmar Border, Suanphung, Ratchaburi, Thailand.
7. An exotic sinusitis.

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*Page*






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DEPARTMENT OF

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## CURRENT RESEARCH ACTIVITIES

Research activities of the Department of Tropical Nutrition and Food Science are concerned with nutritional problems in Thailand, such as micronutrient deficiencies, lifestyle and dietary patterns of different age groups, the impact of overnutrition, oxidative stress and antioxidants in relation to health, especially dislipidemia and coronary heart disease, the effect of smoking on work performance in relation to homocysteine concentration. Furthermore, molecular biology in cancers of the lung, liver, breast cholangiocarcinoma, colon and cervix, including the molecular biology of obesity, were investigated. Food and health relationships in populations of Asian countries are of interest for study, and the data will be compared.

### The topics of the current research projects are as follows:

1. Adiponectin/ACP30, a collagen-like plasma protein, in relation to anthropometric measurement in Thai over-eight and obese subjects.
2. Elevated homocysteine concentrations in healthy Thai smokers related to vitamin status, anthropometric measurements and haematological indices.
3. Methylenetetrahydrofolate reductase (MTHFR) polymor-HISM (C677T) in relation to homo/cysteine concentration in overweight and obese Thai.
4. Relationship between soluble leptin receptor, leptin, lipid profiles and anthropometric parameters in overweight and obese Thai subjects.
5. Riboflavin-deficient and *Trichinella spiralis*-induced stresses on plasma corticos/terone associated with spermatogenesis in male Wistar rats.
6. Serum leptin concentrations in chronic hepatitis.
7. Obesity and related research in Thais.
8. Food habits of women with cervical dysplasia and invasive cervical cancer.
9. Folate status of Thai women with cervical dysplasia.
10. Chromosome 10 and 17 deletions and p53 gene mutations in Thai patients with astrocytomas.
11. Identification of *Cryptosporidium parvum* genotype from HIV and non-HIV fecal samples by PCR.
12. Atherosclerosis and civilization.
13. Ultilization of nutrient sources by female *Anopheles dirus* (Diptera: Culicidae).
14. Identification of DNA amplification in chromosome 9q23-24 in breast cancer.
15. Identification of novel glutathione-5-transferase gene alterations in ovarian cancer.
16. Gene amplification on chromosome 4p15.2 in breast cancer.

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## CURRENT RESEARCH ACTIVITIES

1. Malaria: histopathologic and electronmicroscopic studies on various tissues and organs in humans.
2. Light and electron microscopic correlation of knob proteins and staging *in vitro*: *Plasmodium falciparum*.
3. Pathogenic effects of cytokines and nitric oxide in severe malaria.
4. Endothelial cell activation by *Plasmodium falciparum*.
5. Role of nitric oxide in vascular pathologic changes in atherosclerosis: *in vitro* study.
6. Response of mast cells in falciparum malaria.
7. Cytokines in HIV infection and malaria.

## AWARDS 2004

| No. | Title of Award | Award Recipient | Awarded by | Award Date |
|---|---|---|---|---|
| 1. | Professor Emeritus Khunying Trankchit Harinasuta Award for the Most Outstanding Student of The Doctor of Philosophy in Tropical Medicine Class of 2004 | Miss Jaiaue Wongtanachai | Faculty of Tropical Medicine Mahidol University | 26 June 2004 |
| 2. | Best Student Presentation Award | Miss Nawakanit Sachanonta | Joint International Tropical Medicine Meeting 2004 | 2 December 2004 |

## Highlight Activities

The Department of Tropical Pathology is one of the eleven departments in the Faculty of Tropical Medicine, located on the second floor of the Research Building for Tropical Diseases. The Department is responsible for teaching tropical pathology in the M.Sc./Ph.D. degree programs in tropical medicine, and the D.T.M. & H. course. Short course and training programs related to tropical pathology and electron microscopy are provided occasionally upon request. Research activities have been performed using light microscopy and electron microscopy. Routine services for the Hospital for Tropical Diseases include histopathological diagnosis, cytopathological diagnosis and autopsy. We also welcome surgical specimens for research and diagnosis from other hospitals or institutes. Threee electron microscopes are available for research work on the electron microscopy of tropical diseases and their vectors.

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## CURRENT RESEARCH ACTIVITIES

1. A phase II, pilot, randomized, open-label, single-center study to evaluate immunogenicity and safety after PCECV rabies vaccine (Rabipur®) administered concomitantly with Japanese encephalitis vaccine as a pre-exposure regimen in 12 to 18 month old toddlers in Thailand (M49P2).
2. Evaluation of long-term/immunity against rabies in children vaccinated with Purified Chick Embryo Cell Rabies Vaccine (Rabipur®) in different pre-exposure regimens and boosted after one year (extension of study M49P2).
3. Evaluation of long-term/immunity against Japanese encephalitis in children vaccinated with Japanese encephalitis vaccine (extension of study M49P2).
4. Accuracy assessment of using WHO criteria in diagnosis of dengue infection.
5. Safety and immunogenicity of tetravalent dengue vaccine formulation in Thai adult volunteers: eight-year antibody persistence.
6. Safety and immunogenicity of tetravalent dengue vaccine formulations in healthy Thai children: evaluation of a booster dose and five-year antibody persistence.
7. Epidemiological study of dengue infection in children aged 3-10 years in Ratchaburi Provience.

Highlight Activities

"The major duties of the Department of Tropical Pediatrics are firstly, to disseminate medical knowledge, especially on tropical diseases in pediatrics, to health personnel and the people; secondly, to perform researches and finally, to provide medical services.

The Master of Clinical Tropical Pediatrics program, which includes basic knowledge of tropical diseases, clinical tropical pediatric practice, and a thematic paper, is the major training course of the department. The Department is involved in several training courses of the Faculty.

Each year, there is a one-month course in tropical pediatrics for the fellowship in pediatric infectious diseases training program under the Pediatric Infectious Disease Society of Thailand.

Research topics of the Department are wide in spectrum, including clinical tropical pediatrics, infectious diseases, and vaccine trials."

## LIST OF ABSTRACTS

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**Field of Expertise:** Cultivation and drug sensitivity test of *P. falciparum*
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Cert. On Medical Technology, B.Ed. (General Science)

**Miss Udomluk Thangtaweewaroaj** — Genl. Aff. Off.

B.A. (Medical Secretary)

DEPARTMENT OF

# Tropical Radioisotopes

**Telephone:** 02 643 5585, 02 354 9100-19 ext. 2040, 2041, 2042, 2043, 2044; **Fax:** 02 354 9139

**ASSIST. PROF. CHANNARONG SANGHIRUN** Head of Department

## CURRENT RESEARCH ACTIVITIES

1. The Department's current research is as follows:
   - 1.1 Comparison of non-radiological technique and $^{125}$I-labeled method for measurement of folic acid in normal RBC and sera of patients with cervical dysplasia.
   - 1.2 Comparison of non-radiological technique and $^{125}$I-labeled method for measurement of folic acid in patients with Alzheimer's disease.
   - 1.3 Comparison of non-radiological technique and $^{125}$I-labeled method for measurement of folic acid in normal sera.
   - 1.4 Determination of vitamin $B_{12}$ and folic acid in Thai foods.
   - 1.5 Distribution of $C^{14}$-Labelled arteether in mouse kidney and liver.

2. The Department has cooperated with other departments, as follows :
   - 2.1 $LD_{50}$ of 4 Thai medicinal herbs in mice.
   - 2.2 The correlation between folic acid status and cervical cytologic abnormality in Thai women.
   - 2.3 Established double antibody ELISA method for detection of pathogenic protozoal antigens in feces.

3. The Department has cooperated with the Neuro-Behavioural Biology Center, Institute of Science and Technology for Research and Development in "Determination of Serum Vitamin $B_{12}$ and Folic Acid in Thai Alzheimer's Patients"

4. The Department has cooperated with the Department of Pediatrics, Faculty of Medicine Ramathibodi Hospital in "Homocysteinemia and Thrombosis in Thai Children Patients"


2
ACETYLCHOLINESTERASE AND CHOLINESTERASE ACTIVITIES IN *GIARDIA LAMBLIA* TROPHOZOITES CULTURED *IN VITRO*

## AWARD 2004

The Most Attractive Poster, Second Prize, in the Joint International Tropical Medicine Meeting 2004 was awarded to the Department of Tropical Radioisotopes for "Acetylcholinesterase and Cholinesterase activities in *Giardia lamblia* Trophozoites Cultured *In Vitro*" by the Faculty of Tropical Medicine, in December 2004.

## LIST OF ABSTRACTS

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# Wellcome Unit

**DR. NICHOLAS DAY** Director

## CURRENT RESEARCH ACTIVITIES

The WellcomeTrust-Mahidol University-Oxford Tropical Medicine Research Programme (the 'Thailand Unit') began in 1979 as a research collaboration between the Faculty of Tropical Medicine, Mahidol University and the University of Oxford. Our main administrative office and laboratories are embedded within the Faculty, though most of our clinical studies and much of our laboratory work takes place in 'up-country' study sites. Our main research interests are the epidemiology, diagnosis, pathophysiology and treatment of malaria, scrub typhus, melioidosis, leptospirosis and other tropical infections which impose a substantial disease burden on rural populations throughout this populous region. We have study sites in Ubon Ratchatani (melioidosis and cryptococcal meningitis), Udon Thani (scrub typhus and leptospirosis), Mae Sod Hospital (malaria and microbiological support for SMRU), and Chittagong Medical College in Bangladesh (severe malaria). We also supervise severe malaria clinical trial sites in Burma and India.

## LIST OF ABSTRACTS

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# Vaccine Trial Centre

**ASSOC. PROF. PRATAP SINGHASIVANON** Director

The Vaccine Trial Centre (VTC) was established in February 1984 and has become a full function centre since November 1986. The VTC is a joint responsibility of Mahidol University and the Ministry of Public Health, and operated by the Faculty of Tropical Medicine on their behalf. The major purpose of the centre is for testing newly developed vaccines that reach the clinical trials stage, however, the centre currently expands its service to the pharmaceutical drug development where evaluation in human participants is needed. The VTC has experiences in conducting several Phase I/II and large Phase III trials for various infectious diseases, for example, diarrheal diseases, malaria, HIV, and other viral infections. Currently, the VTC involves in the world largest HIV vaccine community trial with 16,000 healthy informed consented volunteers.

The VTC renders its service in both clinical management and data management of the trial. The centre is the first and the only facility of its kind in Thailand, in the region, and perhaps also in developing countries. The VTC has set its goal since the establishment to ensure that all trials under its responsibility are conducted and documented in accordance with international standards and guidelines including the International Conference on Harmonisation (ICH) / WHO Good Clinical Practice standards. Each function would have pre-established systematic written procedures for the organization, conduct, data collection, data management, documentation and verification of the trial. The clinical trials carried out under VTC are entrusted with the validity of data and the ethical, scientific and technological quality of trials.


## VACCINE TRIAL CENTRE

Floor 10, 11 Chamlong Harinasuta Building
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## DATA MANAGEMENT UNIT

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The VTC sets its mission to collaborate with scientists at any national and international institutes as well as vaccine developers, pharmaceutical companies or donor agencies. The centre provides the necessary infrastructure to enable multi-centre clinical trials and also epidemiological studies to be performed meeting international standards for design, conduct and reporting. The advantage of conducting the trials at VTC is that the centre is equipped with validated system, technology and procedures and that its professional staff is well-trained and has tremendous experiences in trial conduct. The VTC would collaborate with any studies done in Thailand, the immediate region or internationally. The centre accomplishes its mission by planning, implementing and evaluating the study protocol or concepts with mutual cooperative agreements and contracts.

## CURRENT RESEARCH ACTIVITIES:

Screening and Evaluation of Potential Volunteers for a Trial in Thailand of a candidate Preventive HIV Vaccine

A Phase III Trial of Aventis Pasteur Live Recombinant ALVAC-HIV (vCP1521) Priming with VaxGen gp120 B/E (AIDSVAX®B/E) Boosting in HIV-uninfected Thai Adults

Extended evaluation of the virologic, immunologic, and clinical course of volunteers who become HIV-1 infected during participation in a phase III vaccine trial of ALVAC-HIV and AIDSVAX® B/E.

Data Management Unit

# Data Management Unit

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**Dr. Jaranit Kaewkungwal** Chief

The Data Management Unit (DMU) was officially established by the Executive Committee of the Faculty of Tropical Medicine, Mahidol University on 12 March 1999 to fulfill national requirements under the Thailand National AIDS Committee in conducting the first large scale HIV vaccine trial in Thailand. Its establishment and early-year operations were sponsored by VaxGen Inc., Brisbane, CA, U.S.A. Currently, the DMU gets funding and personnel support from the Faculty as well as the national and international pharmaceutical product development industry.

The DMU is functionally under the VTC, the Dean's office, Faculty of Tropical Medicine. In 2002, DMU also rendered services in database development, consultation and training in data management and analysis for biomedical research through the Applied and Technological Service Centre of Mahidol University. The major objectives of the DMU include: (1) To establish a data management excellence centre in Thailand and serve as a reference centre for data management for vaccine and clinical trials in the region, (2) To serve as a collaborating centre for high-quality data management for vaccine and clinical trials within the Faculty and for other institutions, including international collaborators, (3) To provide training for Faculty staff and other institutions in clinical data management that complies with international standards and guidelines, and (4) To advise and/or develop data management and analysis for biomedical research and services.

The ultimate goal of the DMU is set such that its mission will provide data quality for a particular clinical trial or epidemiological study and, if required, data management in a regulatory compliance environment. Thus, the DMU arranges its teamwork in three major areas. Besides the chief, administrative and secretarial staff, the data management personnel are divided into "data quality group", the "information-communication technology (ICT) group" and the "quality assurance group". The numbers of personnel assigned to each group will depend on the complexity and amount of data and workload of the trial.

The DMU mission is accomplished through collaborative agreements, both academic and financial among all parties involved. The Faculty will render all administrative and logistical support to facilitate the operation of the DMU that will enable it to attain high-quality performance. The collaborator(s) would enjoy the benefits of high-standard data management practices.

Currently, the DMU plays major roles in data management of the world's largest HIV vaccine trial, conducted in Thailand. In this trial, all data management processes for over 25,000 volunteers during the 5-year study period are performed within the DMU; and, as this is the first trial in Thailand to maintain a primary database subject to audit by the US FDA, the DMU has utilized highest quality data management technology ever used in the region. Besides this vast experience in data management in a regulated environment according to international standards, the DMU collaborates with other institutions in conducting research studies as well as consultation and database development, for example, database development for quality control and assurance processes for the Department of Medical Science, Ministry of Public Health.

| | | |
|---|---|---|
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# Clinical Trial Section

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## CURRENT ACTIVITIES

1. A Phase III Trial of Aventis Patseur Live Recombinant ALVAC-HIV (vCP1521) Priming with VaxGen gp120 B/E (AIDSVAXTM B/E) Boosting in HIV-uninfected Thai Adults.

## OBJECTIVES:

### Primary Objective

- To determine whether immunization with an integrated combination of ALVAC-HIV (vCP1521) boosted by AIDSVAXTM gp120 B/E prevent HIV infection in healthy Thai volunteers .

### Secondary Objectives

- To determine whether immunization with this vaccine combination results in reduced HIV viral load.
- To determine whether immunization with this vaccine combination results in an increased CD4 count.
- To confirm the safety of vaccine combination in Thai volunteer.
- To evaluate whether participation is associated with behavior change.

## VACCINES:

### Prime:

- ALVAC-HIV (vCP1521) is a recombinant canarypox vector vaccine and HIV-1 gag and protease (subtype B).

### Boost:

- AIDSVAX B/E is a bivalent HIV gp120 envelope glycoprotein vaccine containing a subtype E and a subtype B.

### Study sites:

- 4 clinics in Chonburi Province and 4 clinics in Rayong Province.

2. Immunogenicity and Safety of Quadrivalent HPV (Type 6, 11, 16, 18) L1 Virus Like Particle (VLP) Vaccine in 16 to 23-Year-Old Women With an Immunogenicity Bridge Between the HPV16 component of the Quadrivalent Vaccine and the Monovalent HPV 16 Vaccine Pilot Manufacturing Material—The F.U.T.U.R.E. I Study (Females United to Unilaterally Reduce Endo/ Ectocervical Disease).

## OBJECTIVES:

- To demonstrate that quadrivalent HPV vaccine is generally well tolerated.
- To demonstrate that he Final Manufacturing Process (FMP) results in quadrivalent HPV vaccine.

### Study design:

- 2 groups: a quadrivlent HPV vaccine group and a placebo group.
- Randomized, double-blind, placebo-controlled, multicenter study.

3. Safety, Immunogenicity, and Efficacy of Quadrivalent HPV (Types 6, 11. 16, 18) L1 Virus-Like Particle (VLP) Vaccine in mid-Adult Women—The FUTURE III (Females United To Unilaterally Reduce Endo-Ecto Cervical Cancer) Study.

## OBJECTIVES:

- To demonstrate that a 3-dose regimen of Quadrivalent HPV (Type 6, 11, 16, 18) L1 VLP Vaccine is generally well tolerated in women 24 to 45 year of age.

### Study design:

- 2 groups: a quadrivlent HPV vaccine group and a placebo group.
- Randomized, double-blind, placebo-controlled, multicenter study.



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- Clinical Research Coordinator (CRC)

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Wanwisa Charoensin
Sitawaas Sumrej
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# The Bangkok School of Tropical Medicine

The Bangkok School of Tropical Medicine was established in 1960 to teach Thai medical doctors, especially those working in rural areas, tropical medicine, parasitology and the preventive aspects of endemic diseases. The School now provides continuing education to doctors, researchers, medical personnel and professionals concerned with tropical medicine and public health through its five programs, from postgraduate diploma to PhD levels. English is the medium of instruction. The courses are open to students from all around the world. Details of the School's programs can be viewed on the Faculty's website at: *http://www.tm.mahidol.ac.th* or may be requested by e-mail from the School at e-mail address: *tmedu@diamond.mahidol.ac.th*



## REGULAR POSTGRADUATE PROGRAMS

1. Graduate Diploma in Tropical Medicine and Hygiene

   The course provides medical doctors with the concepts and principles of clinical management of tropical diseases, epidemiology, prevention and control, and health problems in tropical areas.

2. Master of Clinical Tropical Medicine and Master of Clinical Tropical Pediatrics

   The M.C.T.M. program is an extension of the D.T.M.&H. Its purpose is to train medical doctors in tropical and endemic diseases in relation to their causes, epidemiology, pathogenic mechanisms, prevention and control; to be able to efficiently examine, diagnose and treat patients suffering from tropical and endemic diseases; to be able to provide consultation, disseminate and impart knowledge of tropical medicine; and, competently to conduct clinical research.

3. Master of Science in Tropical Medicine

   This program develops competency in research, and the capacity to deliver technical services related to tropical medicine. There are 14 major fields: clinical tropical medicine, clinical pharmacology, epidemiology, microbiology, immunology, biochemical nutrition, nutritional epidemiology, nutritional toxicology, tropical pathology, radiological science, social medicine, environmental toxicology, environmental health, parasitology, and medical entomology.

4. Doctor of Philosophy in Tropical Medicine

   This doctoral program provides advanced knowledge and skills for competency in research, particularly in tropical medicine. There are 14 major fields, as for the Master of Science in Tropical Medicine, listed above.

5. Doctor of Philosophy in Clinical Tropical Medicine

This program enables medical doctors to gain advanced knowledge, study new techniques, and apply them to areas of research in clinical tropical medicine. Students conduct an original extensive research project related to clinical tropical medicine.

## COLLABORATIVE TRAINING PROGRAMS

### Master of Science in Clinical Epidemiology

The Faculty, with the Faculties of Public Health and Medicine, Ramathibodhi Hospital, offers this international program. The objective is to develop academic and health service leadership, which will facilitate effective public health and medical care programs at every level in various countries.

## GRADUATE DIPLOMA IN TROPICAL MEDICINE AND HYGIENE

### PHILOSOPHY

The program emphasizes producing graduates with an in-depth knowledge of tropical medicine and hygiene. Graduates will be able to manage, and provide consultation on, common health problems and diseases in the tropics.

### OBJECTIVES

1. To produce graduates with a good level of knowledge of tropical health problems and diseases, including epidemiology, etiology, pathogenesis, pathology, nutritional aspects, risk factors, and clinical manifestations.
2. To produce graduates with the competency to manage common health problems and diseases in the tropics, including diagnosis, treatment, prevention, control, and providing consultation.

This program is fully accredited by the American Society of Tropical Medicine and Hygiene (A.S.T.M.H.), is offered in the English language, and is open to participants of all nationalities.

### ADMISSION REQUIREMENTS

1. Students must hold a M.D., M.B.B.S., or other qualification as a qualified medical doctor accepted by Mahidol University.
2. Pass the English Proficiency Examination according to the requirements of the Faculty of Graduate Studies, Mahidol University.

**Note 1**: Applicants should have a TOEFL English language proficiency level of 500 or more or an IELTS score level of 5.5 or more.

**Note 2**: Exceptions may be made by the Program Committee and the Dean of the Faculty of Graduate Studies. Other categories of student may be permitted to attend, and be provided with a "Certificate of Attendance".

**DURATION OF STUDY** 6 months, April-September each year.

## MASTER OF CLINICAL TROPICAL MEDICINE

### INTRODUCTION

The Bangkok School of Tropical Medicine offers the international Master of Clinical Tropical Medicine program (M.C.T.M.) from the first week in April each year. The program is offered in English and is open to students of all nationalities.

### OBJECTIVES

The M.C.T.M. was established to train medical graduates to be:

1. Well-versed and well-informed in tropical and endemic diseases with special reference to Southeast Asia in relation to their causes, epidemiology, pathogenic mechanisms, and prevention and control of diseases.
2. Able to efficiently examine, diagnose and treat the patients suffering from tropical and endemic diseases.
3. Able to provide consultation, and disseminate and impart knowledge of Tropical Medicine.
4. Able to conduct clinical research with special emphasis on problem solving that will lead to the autonomous initiation of new knowledge, and also to innovation and continuous academic advancement.

### ADMISSION REQUIREMENTS

**An applicant is required to:**

1. Be a qualified, registered medical doctor, preferably with at least one year's clinical experience.
2. Be physically and mentally healthy;
3. Be proficient in English (reading, writing, speaking, listening).

English language proficiency requirements are as follows: TOEFL score of at least 500 or an IELTS score of at least 6.0. If it is not possible to undergo TOEFL or IELTS testing before commencing the program, applicants will be enrolled as trial students, who will be required to pass the English Language Proficiency Examination of Mahidol University before graduation.

4. Persons who do not have the complete qualifications according to these regulations will be considered by the Postgraduate Committee of the Faculty of Tropical Medicine.

### DURATION OF STUDY

12 months, from the first week of April until the last week of March the following year.

## MASTER OF CLINICAL TROPICAL PEDIATRICS

### INTRODUCTION

The Bangkok School of Tropical Medicine offers the international Master of Clinical Tropical Pediatrics (M.C.T.P) program every year, from the first week in April. The program is taught in English and open to students of all nationalities.

### PHILOSOPHY

The program places its emphasis on training medical graduates to be able to understand the diseases related to tropical pediatrics, with reference to endemic diseases, particularly in Southeast Asia, including etiology, incidence, pathogenesis, clinical features, prevention and control, and to continuing their medical education, which is in accordance with the national education developmental plan.

### OBJECTIVES

To train medical doctors who have basic knowledge in pediatrics, to be able to:

A. Plan appropriate investigations and manage common pediatric infectious diseases efficiently and effectively, with emphasis on tropical and endemic areas,

B. Be consultants and transfer their knowledge of tropical pediatrics to other health personnel,

C. Integrate curative services with preventive measures, including child health promotion,

D. Plan and conduct research according to the proposed methodology, data analysis and writing up of the thematic paper related to pediatric tropical diseases. Afterwards, students will be able to conduct research efficiently and effectively, to improve the health status of the people in their own countries,

E. Use and evaluate epidemiological data and medical biostatistics in solving child health problems,

F. Use information technology to locate and update knowledge for continuing medical education related to tropical pediatrics,

G. Possess responsibility, integrity, good morals and self-sacrifice for the welfare of the community.

### ADMISSION REQUIREMENTS

**Students must:**

1. Hold a M.D., M.B.B.S. or other equivalent qualification that qualifies them to practice as a medical doctor, which is accepted by Mahidol University and have clinical experience in pediatrics of not less than 1 year.
2. Graduated in the D.T.M.&H., or equivalent, of which credit transfer may be considered by the Program Committee and the Dean of the Faculty of Graduate Studies.
3. Have good mental and physical health.
4. Pass the English Proficiency Examination offered by the Faculty of Graduate Studies, Mahidol University, or other qualified institutions, or have a TOEFL score of 500 or more.
5. For plan A(2) students should have a basic knowledge of clinical research by attending the research methodology and basic statistics for medical research.
6. Exceptions to the above items may be made by the Program Committee and the Dean of the Faculty of Graduate Studies.

### DURATION OF STUDY

12 months, from the first week of April until the last date of March the following year.

## MASTER OF SCIENCE IN TROPICAL MEDICINE
[M.Sc. (Trop.Med.)]
&
## DOCTOR OF PHILOSOPHY IN TROPICAL MEDICINE
[Ph.D. (Trop.Med.)]

### OBJECTIVES

To build appropriate knowledge and skills for competency in research and the ability to deliver technical services related to tropical medicine, and, for the Ph.D., also to meet the urgent need to produce researchers who have in-depth knowledge and specialties in the field of tropical medicine and are capable of planning and undertaking research projects effectively.

### ADMISSION REQUIREMENTS

**For the M.Sc.**, applicants must hold an M.D., D.D.S., D.V.M., B. Pharmacy or B.Sc. degree.

**For the Ph.D. Plan 1**, applicants must hold:

1. M.Sc. in Tropical Medicine or related field, or
2. M.D., D.V.M., or D.D.S., and have at least 2 research publications, one as the first author, in a recognized journal.

**For the Ph.D. Plan 2**, applicants must hold:

1. M.Sc., M.D., D.V.M., or D.D.S., or

2. Be an M.Sc. (Trop.Med.) student who has completed the first year core subjects with a GPA of not less than 3.5, or hold a B.Sc. (Hon.).

3. Before enrolment into one of the above programs, an applicant must be accepted by an appropriate advisor.

4. Applicants should have a TOEFL English language proficiency level of 500 or more.

5. To graduate, all non-native English speakers must pass the English Language Proficiency Examination according to the requirements of the Faculty of Graduate Studies, Mahidol University.

6. Exceptions may be made by the Program Committee and the Dean of the Faculty of Graduate Studies.

### DURATION OF STUDY

**For the M.Sc.**, a minimum of 2 years full-time and a maximum of 5 years.

**For the Ph.D. Plan 1**, a maximum of 5 years.

**For the Ph.D. Plan 2**, a maximum of 5 years for holders of an M.Sc., and a maximum of 8 years for holders of a B.Sc.

### COMMENCEMENT

Normally the first Monday of June each year. There is another intake in November each year, by arrangement.

## DOCTOR OF PHILOSOPHY IN CLINICAL TROPICAL MEDICINE

### INTRODUCTION

The Doctor of Philosophy in Clinical Tropical Medicine is offered by the Bangkok School of Tropical Medicine every year. The program is offered in English and is open to students of all nationalities. The aim of the course is to produce medical graduates at Ph.D. level who are competent in performing research leading to the solution of clinical problems in the Tropics, and to improving the quality of life of the people of tropical countries, particularly Thailand and Southeast Asia.

### OBJECTIVES

To provide appropriate knowledge and skills for competency in research and the ability to deliver technical services related to tropical medicine and also to meet the urgent need for researchers who have in-depth knowledge and specialities in the field of tropical medicine and are capable of planning and undertaking research projects effectively.

**DURATION OF STUDY** Not more than 5 years.

## ADMISSION REQUIREMENTS

### A. PLAN I

**Candidates are required to:**

1. Be certified in clinical specialties by the Board of the Thai Medicine Council, or its equivalent; and hold the Graduate Diploma in Tropical Medicine and Hygiene (D.T.M.&H.) from Mahidol University, or its equivalent;

2. Hold a license for general medicine (first class) in their domicile countries or in the countries where they graduated and held a license and have had a clinical appointment in a hospital for at least one year;

3. Have passed TOEFL with a score not less than 500 or have obtained an IELTS score of not less than 6.0 and not more than 2 years from the application date.

### B. PLAN II

1. Hold the Master of Clinical Tropical Medicine (M.C.T.M..) degree from Mahidol University, or its equivalent;

2. Hold a license for general medicine (first class) in their domicile countries or in the countries where they graduated and held a license and have had a clinical appointment in a hospital for at least one year;

3. Have passed TOEFL with a score not less than 500 or have obtained an IELTS score of not less than 6.0 and not more than 2 years from the application date.

## The Bangkok School of Tropical Medicine

Course Participants 2004

### D.T.M. & H.

| | | |
|---|---|---|
| 1. | Dr. Sandra Olive Morelle Davies | Australia |
| 2. | Dr. Muhammad Shaukat Haidar | Bangladesh |
| 3. | Dr. Md. Fakhrul Alam | Bangladesh |
| 4. | Dr. Mohammed Enamul Hoque | Bangladesh |
| 5. | Dr. Ngoun Chan Pheaktra | Cambodia |
| 6. | Dr. Setthi Chhea | Cambodia |
| 7. | Dr. Aneley Getahun Strobel | Ethiopia |
| 8. | Dr. Rhitam Chakraborty | India |
| 9. | Dr. Hartini Sugianto | Indonesia |
| 10. | Dr. Shigeki Hanafusa | Japan |
| 11. | Dr. Takeshi Matsumura | Japan |
| 12. | Dr. Shinya Shirai | Japan |
| 13. | Dr. Bouakham Vannachone | Lao P.D.R. |
| 14. | Dr. Myat Thura | Myanmar |
| 15. | Dr. Khine Thinzar | Myanmar |
| 16. | Dr. Zay Yar Nyo Htay | Myanmar |
| 17. | Dr. Tun Aung Kyaw | Myanmar |

**D.T.M. & H.** (Continued)

| | | |
|---|---|---|
| 18. | Dr. Raya Cruz Constantino | Philippines |
| 19. | Dr. Alvaro Cervera | Spain |
| 20. | Dr. Susith Ranjan Wadikage | Sri Lanka |
| 21. | Dr. Yves Jackson | Switzerland |
| 22. | Dr. Malek (Daniel) Touabi | Switzerland |
| 23. | Dr. Parueluk Kesorn | Thailand |
| 24. | Dr. Wirongrong Charoenpong | Thailand |
| 25. | Dr. Suwimol Jearraksuwan | Thailand |
| 26. | Dr. Benjaporn Tuntasood | Thailand |
| 27. | Dr. Raweerat Sitcharungsi | Thailand |
| 28. | Dr. Supadanu Oddie Sriratana | Thailand |
| 29. | Dr. Viravarn Luvira | Thailand |
| 30. | Dr. Abdu-Rahman Mohamed Nuh | U.A.E. |
| 31. | Dr. Eleanor Clotilde Heylen | U.K. |
| 32. | Mrs. Jean Buckley | U.S.A. |

**M.T.C.M.**

| | | |
|---|---|---|
| 1. | Dr. Aneley Getahun Strobel | Ethiopia |
| 2. | Dr. Rhitam Chakraborty | India |
| 3. | Dr. Bouakham Vannachone | Lao P.D.R. |
| 4. | Dr. Zay Yar Nyo Htay | Myanmar |
| 5. | Dr. Malek Daniel Touabi | Switzerland |

**M.C.T.P.**

| | | |
|---|---|---|
| 1. | Dr. Susith Ranjan Wadikage | Sri Lanka |
| 2. | Dr. Abdu-Rahman Mohamed Nuh | U.A.E. |

**M.SC. (TROP.MED.)**

1st year students

| | | |
|---|---|---|
| 1. | Miss Intira Pipitgool | Thailand |
| 2. | Miss Nipaporn Tewawong | Thailand |
| 3. | Mr. Panupong Sahaisook | Thailand |
| 4. | Miss Pichayanut Poolperm | Thailand |
| 5. | Miss Sunisa Malijunboa | Thailand |
| 6. | Mr. Nattavut Wongdeethai | Thailand |
| 7. | Maj. Orawan Nunthamongkol | Thailand |
| 8. | Miss Kulrat Chitcharoenrung | Thailand |
| 9. | Miss Somrudee Attachit | Thailand |
| 10. | Miss Juntima Sritabal | Thailand |
| 11. | Miss Sudaporn Kengkarn | Thailand |

**M.SC. (TROP.MED.)** (Continued)

1st year students

| | | |
|---|---|---|
| 12. | Miss Tawiwan Sareebot | Thailand |
| 13. | Miss Aucha Sachair | Thailand |
| 14. | Miss Patcharee Khongtak | Thailand |
| 15. | Miss Ampai Tanganuchitcharnchai | Thailand |
| 16. | Mr. Nitipan Tantawiwattananon | Thailand |
| 17. | Miss Pornapat Surasombatpattana | Thailand |
| 18. | Miss Charoonluk Sangloung | Thailand |
| 19. | Miss Warangkana Lektrakul | Thailand |
| 20. | Miss Issariya Ieamsuwan | Thailand |
| 21. | Mr. Dilok Tongsukh | Thailand |
| 22. | Miss Khwananong Youngpakool | Thailand |
| 23. | Mr. Kata Gunlabun | Thailand |
| 24. | Miss Siriluk Feangvad | Thailand |
| 25. | Miss Tippawan Sungkapong | Thailand |
| 26. | Miss Sriwipa Chuangchaiya | Thailand |
| 27. | Dr. Mohammad Jahirul Karim | Bangladesh |
| 28. | Dr. Biraj Man Karmacharya | Nepal |
| 29. | Miss Rie Takeuchi | Japan |

**PH.D. (TROP.MED.)**

1st year students

| | | |
|---|---|---|
| 1. | Mrs. Narisara Chantratita | Thailand |
| 2. | Dr. Suthat Chottanapund | Thailand |
| 3. | Mrs. Kritsana Janyapoon | Thailand |
| 4. | Miss Chuthaporn Tongboonchoo | Thailand |
| 5. | Miss Ruangrat Buddhirongawatr | Thailand |
| 6. | Miss Pannamthip Pitaksajjakul | Thailand |
| 7. | Miss Suchada Sumroiphon | Thailand |
| 8. | Miss Nuananong Jirakanjanakit | Thailand |
| 9. | Miss Parichat Lapcharoen | Thailand |
| 10. | Mr. Kasem Somthana | Thailand |
| 11. | Dr. Srivicha Krudsood | Thailand |
| 12. | Mrs. Areerat Sa-ngasang | Thailand |
| 13. | Miss Pranom Kunsakorn | Thailand |
| 14. | Dr. Suttinun Chantanakul | Thailand |
| 15. | Mr. Yudthana Samung | Thailand |
| 16. | Mr. Patthanasak Khammaneechan | Thailand |
| 17. | Miss Somsiri Decharat | Thailand |
| 18. | Dr. Md. Mushfiqur Rahman | Bangladesh |

## Thesis Titles

### M.C.T.M. (THEMATIC PAPERS)

| Department | Name | Title of Thesis | Advisor |
|---|---|---|---|
| Clinical Tropical Medicine | Dr. Aneley Getahun Strobel | Efficacy and safety of fixed-dose combination of stavudine, lamivudine and nevirapine (GPO-VIR$^{R}$) in the treatment of AIDS. | Assoc. Prof. Punnee Pitisuttithum |

## M.C.T.M. (THEMATIC PAPERS) (Continued)

| Department | Name | Title of Thesis | Advisor |
|---|---|---|---|
| Clinical Tropical Medicine | Dr. Rhitam Chakraborty | An evaluation of cryptococal meningitis in HIV/AIDS patients with sequential amphotericin B plus oral fluconazole. | Assoc. Prof. Punnee Pitisuttithum |
| Clinical Tropical Medicine | Dr. Bouakham Vannachone | Scrub typhus in acute febrile illness patients with neurological manifestation. | Assist. Prof. Udomsak Silachamroon |
| Clinical Tropical Medicine | Dr. Zay Yar Nyo Htay | An evaluation of cryptococal meningitis in HIV/AIDS patients with sequential amphotericin B plus oral fluconazole. | Dr. Wichai Ekataksin |
| Clinical Tropical Medicine | Dr. Malek Daniel Touabi | Sensitivity of *Plasmodium falciparum* to artemisinin: an *in vivo* and *in vitro* descriptive study. | Prof. Polrat Wilairatana |

## M.C.T.P. (THEMATIC PAPERS)

| Department | Name | Title of Thesis | Advisor |
|---|---|---|---|
| Tropical Pediatrics | Dr. Susith Ranjan Wadikage | Risk factors for methicillin-resistant *Staphylococcus aureus* infection at Queen Sirikit National Institute of Child Health. | Assist. Prof. Kriengsak Limkittikul |
| Tropical Pediatrics | Dr. Abdu-Rahman Mohamed Nuh | Risk factors for methicillin-resistant *Staphylococcus aureus* infection at Queen Sirikit National Institute of Child Health. | Dr. Keswadee Lapphra |

## M.SC. (TROP.MED.)

| Department | Name | Title of Thesis | Advisor |
|---|---|---|---|
| Protozoology | Mr. Tawin Inpankaew | Zoonotic canine giardiasis in temple-related communities in Bangkok, Thailand. | Assoc. Prof.Yaowalark Sukthana |
| Clinical Tropical Medicine | Miss Forradee Nuchsongsin | Rigidify factors involving in reduction of erythrocyte deformability in falciparum malaria. | Assist. Prof. Kesinee Chotivanich |
| Microbiology and Immunology | Miss Yuphin Kongprai | Study of the membrane protein antigen of leptospira that react with leptospirosis patients. | Assist. Prof. Thareerat Kalambaheti |
| Microbiology and Immunology | Miss Sineewanlaya Wichit | Identification of receptor molecule for dengue virus from mosquito cell line. | Assoc. Prof. Wipawee Usawattanakul |
| Microbiology and Immunology | Mr. Supapong Attasri | Antibody profile to recombinant EB200 of *Plasmodium falciparum* 332 antigen induced by natural infection. | Prof. Srisin Khusmith |
| Tropical Nutrition & Food Science | Mr. Sujan Babu Marahatta | Polymorphism of glutathione S-transferase Omega *(GSTO)* gene and risk of cancer among Thai patients. | Assoc. Prof. Songsak Petmitr |
| Microbiology and Immunology | Mr. Bishnu Prasad Upadhyay | Detection of *Salmonella* in seafood samples by modified semisolid Rappaport-Vassiliadis method and PCR-based assay. | Prof. Srisin Khusmith |
| Microbiology and Immunology | Mr. Dhruba Kumar Khadka | Identification of the mutation in *KAT G* and *INH A* genes of isoniazid resistant Mycobacterium tubercuosis. | Prof. Srisin Khusmith |

## M.SC. (TROP.MED.) (Continued)

| Department | Name | Title of Thesis | Advisor |
|---|---|---|---|
| Microbiology and Immunology | Miss Kaesinee Phuwao | Cloning, expression and purification of pyruvate: ferredoxin oxidoreductase (PFOR) of *Entamoeba histolytica*. | Assoc. Prof. Nitaya Thammapalerd |
| Tropical Hygiene | Pol. Maj. Kitanapa Napakorn | Trends and factors related to road traffic fatal crash in Thailand using police databases. | Assoc. Prof. Pratap Singhasivanon |
| Microbiology and Immunology | Miss Chanthanee Nitigaroon | PCR diagnosis of amoebiasis. | Assoc. Prof. Nitaya Thammapalerd |
| Microbiology and Immunology | Miss Jiraporn Kuljiraruk | Effect of holarrhena antidysenterica extract on the growth of local Thai isolate of *Entamoeba histolytica* HTH-56: MUTM. | Assoc. Prof. Nitaya Thammapalerd |
| Microbiology and Immunology | Miss Thipawan Kanghae | Idenification of *Legionella* spp. isolated in Thailand by 16S rDNA PCR-restriction fragment length polymorphism. | Assist. Prof. Usanee Suthisarnsuntorn |
| Microbiology and Immunology | Miss Nada Petabut | Antibody response profile to *P. vivax* merozoite surface protein 1 (MSP1) in naturally exposed malaria individuals in Thailand. | Prof. Srisin Khusmith |
| Microbiology and Immunology | Miss Preeyaporn Monatrakul | An application of nested polymerase chain reaction in detecting scrub typhus DNA from clinical specimens. | Assist. Prof. Varee Wongchotigul |
| Tropical Nutrition & Food Science | Miss Pattamaporn Sirima | Identification of gene loss in breast cancer by gene cloning and sequencing. | Assoc. Prof. Songsak Petmitr |
| Tropical Nutrition & Food Science | Miss Piyawan Sricharoen | Adiponectin/ACRP30, a collagen-like plasma protein in relation to anthropometric measurement in Thai overweight and obese subjects. | Assoc. Prof. Rungsunn Tungtrongchitr |
| Microbiology and Immunology | Miss Sirirat Jintagarnrasri | T cell proliferative response to THZR variants on *Plasmodium falciparum* circumsporozoite protein. | Prof. Srisin Khusmith |
| Microbiology and Immunology | Miss Pedcharad Satheanmethakul | Molecular characterization of *Leptospira* species by restriction fragment length polymorphism. | Assist. Prof. Thareerat Kalambaheti |
| Microbiology and Immunology | Mr. Phiromsak Phattanapaigitkun | Cloning, expression and monoclonal antibodies production of VP19 of white spot syndrome virus (WSSV) in black tiger shrimp *(Penaeus monodon)*. | Assoc. Prof. Nitaya Thammapalerd |
| Microbiology and Immunology | Dr. Do Hoang Long | Molecular typing of *Leptospira* species. | Assist. Prof. Thareerat Kalambaheti |
| Microbiology and Immunology | Mr. Chalermpon Kaewjai | Detection of *Acanthamoeba* spp. by using polymerase chain reaction (PCR) assays. | Assoc. Prof. Nitaya Thammapalerd |
| Clinical Tropical Medicine | Miss Nattawan Rachapaew | *In vitro* cultivation of *Plasmodium vivax* and determination of gametocyte maturation using gametocyte stage-specific markers. | Assist. Prof. Kesinee Chotivanich |
| Microbiology and Immunology | Miss Busakorn Promsarin | Detection of virulence factors from *Aeromonas* spp. in relation to diarrhea. | Assoc. Prof. Yuvadee Mahakunkijcharoen |
| Tropical Nutrition & Food Science | Miss Tanyalak Khuntamoon | Local brand canine dry foods and risk of chronic diseases in rats. | Assist. Prof. Karunee Kwanbunjan |

## M.SC. (TROP.MED.) (Continued)

| Department | Name | Title of Thesis | Advisor |
|---|---|---|---|
| Helminthology | Pol. Capt. Natsuda Jamornthanyawat | The immunoblot differentiation of human small fluke infections using *Opisthorchis viverrini* liver fluke and snail antigens. | Assoc. Prof. Jitra Waikagul |
| Helminthology | Miss Penapa Yutayong | *Toxocara canis* larval antigens for serodiagnosis of human toxocariosis. | Assoc. Prof. Wichit Rojekittikhun |
| Tropical Hygiene | Miss Nahathai Chulakarat | Sputum conversion among newly adult positive-smear pulmonary tuberculosis patients. | Assoc. Prof. Pratap Singhasivanon |
| Tropical Hygiene | Miss Piyaporn Suebtrakul | A health survey of primary school using a geographic information system (GIS) in Sai yok District, Kanchanaburi. | Assoc. Prof. Pratap Singhasivanon |

## PH.D. (TROP.MED.)

| Department | Name | Title of Thesis | Advisor |
|---|---|---|---|
| Clinical Tropical Medicine | Mrs. Narisara Chantratita | Phonotypic plasticity of clinical Burkholderia pseudomallei isolates. | Prof. Sasithorn Pukritiyakamee |
| Tropical Pathology | Mr. Kraisorn Sappayatosok | Expression of NOS, VEGF, COX-2 and their clinico-pathological correlation in oral and para-oral squamous cell carcinoma. | Assist. Prof. Urai Chaisri |
| Microbiology and Immunology | Miss Natharinee Horata | Polymorphism and function of PfEMP1 extracellular domains in Thai *Plasmodium falciparum* isolates causing severe and uncomplicated malaria. | Prof. Srisin Khusmith |
| Protozoology | Mr. Aongart Mahittikorn | Molecular and immunohistochemistry studies on tachyzoite and bradyzoite | Assoc. Prof.Yaowalark Sukthana |
| Medical Entomology | Mr. Apiwat Tawatsin | Novel insect repellents derived from phytochemicals extracted from plants in Thailand. | Assoc. Prof. Narumon Komalamisra |
| Microbiology and Immunology | Miss Pornsawan Amarapal | Role of Tat gene in pathogenesis of HIV infection. | Assoc. Prof. Surang Tantivanich |
| Tropical Radioisotopes | Miss Pachuen Potup | Immunoglobulin class switching induced by *Plasmodium falciparum in vitro*. | Assoc. Prof. Yaowapa Maneerat |
| Microbiology and Immunology | Miss Piyada Wangroongsarb | Molecular characterization of *Leptospira* isolates in Thailand. | Assist. Prof. Thareerat Kalambaheti |
| Tropical Radioisotopes | Dr. Piyanuch Preechapornkul | Quantitative *Ex-vivo* studies of genotypic and phenotypic variation in *Plasmodium falciparum*. | Prof. Sasithorn Pukritiyakamee |
| Tropical Pathology | Miss Doungdaw Nuntakomon | Microparticles in the blood circulation and pathogenesis in severe malaria. | Assist. Prof. Kesinee Chotivanich |
| Microbiology and Immunology | Miss Chintana Phawong | Chemokine gene polymorphisms and their susceptibility to tuberculosis. | Prof. Srisin Khusmith |
| Medical Entomology | Mr. Narong Nitatpattana | Risk of Japanese encephalitis virus domestic transmission in Thailand: virological and entomological approach. | Assoc. Prof. Chamnarn Apiwathnasorn |

## PH.D. (TROP.MED.) (Continued)

| Department | Name | Title of Thesis | Advisor |
|---|---|---|---|
| Social and Environmental Medicine | Miss Manirat Therawiwat | Community-based approach for prevention and control of dengue haemorrhagic fever in Kanchanaburi, Thailand. | Assoc. Prof. Wijitr Fungladda |
| Clinical Tropical Medicine | Miss Naowarat Tanomsing | *Plasmodium malariae*: isolation and characterization of dihydrofolate reductase-thymidylate synthase gene. | Dr. Mallika Imwong |
| Tropical Hygiene | Dr. Trinh Van Hung | Prevalence, risk factors and burden of mortality of road traffic accidents in Thai Nguyen, Vietnam. | Assoc. Prof. Pratap Singhasivanon |
| Tropical Hygiene | Dr. Kittipong Kongsomboon | Spatial pattern and temporal trend of DF/DHF in Thailand: age-period-cohort analysis. | Assoc. Prof. Pratap Singhasivanon |
| Social and Environmental Medicine | Miss Chomrach Sirigul | Rapid quantification of the aerosol *Legionella* spp. using the combination of air sampling and real time polymerase chain reaction technique. | Assist. Prof. Pongrama Ramasoota |
| Microbiology and Immunology | Miss Piyatida Tangteerawatana | Cytokine gene polymorphisms in severe malaria. | Prof. Srisin Khusmith |
| Microbiology and Immunology | Mrs. Panita Gosi | Gene polymorphic analysis of *Plasmodium vivax* duffy binding protein of Thai isolates and their functional capacity in B and T cell activation. | Prof. Srisin Khusmith |
| Medical Entomology | Miss Pruksa Nawtaisong | Analysis of ribozyme strategies for suppression of dengue virus in transgenic *Aedes albopictus*. | Assoc. Prof. Narumon Komalamisra |
| Protozoology | Miss Phuangphet Waree | The electron microscopy study on effects of pyrimethamine artesunate on *Toxoplasma gondii* in animal model. | Assoc. Prof.Yaowalark Sukthana |
| Social and Environmental Medicine | Miss Malee Geounuppakul | An empowerment program to enhance women's ability to prevent and control malaria in Mae Hong Son Province, Thailand. | Assoc. Prof. Piyarat Butraporn |
| Tropical Nutrition & Food Science | Mrs. Sirimon Chaikate | Serum C reactive protein, interleukin-6, tumour necrosis factor-a, lipid profiles, and anthropometric assessment in overweight Thais and healthy controls. | Assoc. Prof. Supranee Changbumrung |
| Medical Entomology | Miss Sirima Kitvatanachai | Laboratory and field determination of lead toxicity in *Culex quinquefasciatus*. | Assoc. Prof. Chamnarn Apiwathnasorn |
| Tropical Nutrition & Food Science | Miss Sunanta Chariyalertsak | Determination of genetic alterations in cholangiocarcinoma using arbitrarily primed polymerase chain reaction and gene cloning. | Assoc. Prof. Songsak Petmitr |
| Tropical Nutrition & Food Science | Mr. Surapon Tangvarasittichai | Mutagenicity and antimutagenicity of fractions of some plant extracts and their molecular formulas. | Assoc. Prof. Supranee Changbumrung |

## PH.D. (TROP.MED.) (Continued)

| Department | Name | Title of Thesis | Advisor |
|---|---|---|---|
| Tropical Hygiene | Dr. Sompong Srisaenpang | Burden and trend of infectious tuberculosis patients, their treatment outcomes and associated factors for treatment success at Khon Kaen Medical School during 1997-2001. | Assoc. Prof. Pratap Singhasivanon |
| Clinical Tropical Medicine | Miss Pannapa Susomboon | Studying endothelial cell activation following *Plasmodium falciparum*-infected erythrocyte binding *in vitro*. | Prof. Sornchai Looareesuwan |
| Helminthology | Mrs. Doungrat Riyong | Purification of *Dirofilaria immitis* antigens for serodiagnosis of Bancroftian filariasis. | Assoc. Prof. Jitra Waikagul |
| Tropical Nutrition & Food Science | Miss Siriporn Chanchay | Resistin and insulin in type II diabetes mellitus obese Thais. | Assoc. Prof. Rungsunn Tungtrongchitr |
| Tropical Nutrition & Food Science | Miss Kanjana Suriyaprom | Homocysteine, B vitamins, vitamin C and dietary pattern in healthy Thai smokers: as risk factors of cardiovascular diseases. | Assoc. Prof. Rungsunn Tungtrongchitr |
| Tropical Hygiene | Miss Verena Ilona Carrara | Epidemiological impact of the large scale deployment of early diagnosis and combination treatment of falciparum malaria on the northwestern border of Thailand; The Tak Malaria Initiative. | Assoc. Prof. Pratap Singhasivanon |
| Clinical Tropical Medicine | Dr. Kim Jung Ryong | The identification of genetype variation of *P.vivax* and mixed infection (*P.v.* and *P.f.*) by the PCR technique in malaria-endemic populations in central Calcutta, India | Prof. Sasithorn Pukritiyakamee |
| Social and Environmental Medicine | Miss Nantawan Kaewpoonsri | Comprehension of volunteers participating in clinical trial. | Assoc. Prof. Kamolnetr Okanurak |
| Microbiology and Immunology | Miss Petchara Tussana | Serogrouping of *Leptospira* spp. by DNA technology. | Assist. Prof. Thareerat Kalambaheti |
| Microbiology and Immunology | Mr. Rongdej Tungtrakanpoung | Leptospirosis vaccine designed using T7 phage display technique. | Assist. Prof. Pongrama Ramasoota |
| Helminthology | Mrs. Tippayarat Yoonuan | *Paragonimus westernmani* and paragonimiasis in Tha Ma Prang, Kaeng Khoi District, Saraburi Province. | Assoc. Prof. Jitra Waikagul |
| Tropical Nutrition & Food Science | Mr. Tanett Pakeetoot | Identification of genetic alterations in breast cancer by arbitrarily primed polymerase chain reaction and gene cloning. | Assoc. Prof. Songsak Petmitr |
| Tropical Pathology | Miss Thanida Tangwanicharoen | Immunohistopathological studies of cytokine profiles in liver tissue of AIDS and HIV-infected patients: a necropsy study. | Assist. Prof. Urai Chaisri |
| Social and Environmental Medicine | Mrs. Pimsurang Taechaboonsermsak | Health-promoting behavior model and quality of life among cervical cancer patients undergoing radiotherapy. | Assist. Prof. Jaranit Kaewkungwal |
| Protozoology | Mr. Zulhainan Bin Hamzah | Development of differential diagnosis of *Entamoeba histolytica*, *Entamoeba dispar* and *Entamoeba moshkovskii* based on random amplified polymorphic DNA technique. | Assoc. Prof. Porntip Petmitr |

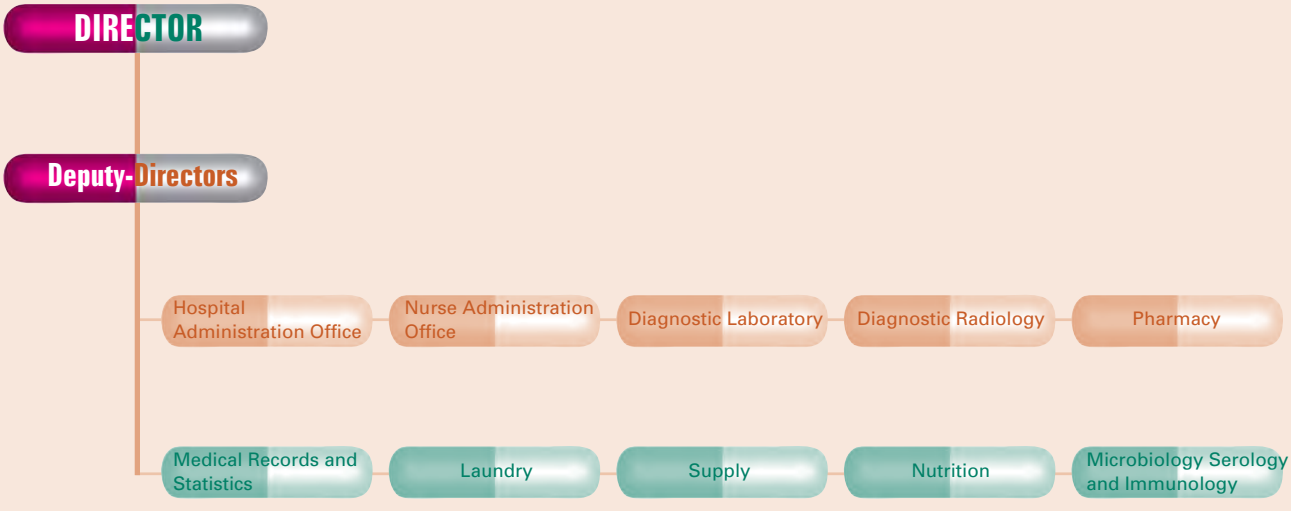
# The Hospital for Tropical Diseases

**Telephone:** 0-2354-9154, 0-2354-9100-19 ext. 1624, 1625

**ASSOC. PROF. WATTANA LEOWATTANA** Director

The Hospital for Tropical Diseases (HTD), a specialized research hospital, is one of the three hospital of Mahidol University, has operated since 1961. The HTD is an administrative structure at the Faculty of Tropical Medicine, Mahidol University that brings together a diverse group of faculty, staff and students from several different specialist whose research and teaching is focused on human pathogens and their invertebrate and vertebrate vectors, the diseases caused by these organisms, and the impact of these diseases on human society. Members of HTD are concerned in particular with the impact of infectious diseases in less developed parts of the world, and research interests of center members range from biomedical science to issues of human rights. Center members also work on new and emerging infectious diseases of importance in the tropical countries, especially those like Severe Acute Respiratory Syndrome (SARS) and Avia flu disease whose public health impact is significantly influenced by human impacts on the environment. Among the diseases studied at HTD are malaria, toxoplasmosis, tuberculosis, lymphatic filariasis, leishmaniasis, dengue, leptospirosis, and scrub typhus. Many faculty work specifically on arthropod vectors, particularly mosquito vectors of arboviruses, filarial worms, and malarial parasites.

## ORGANIZATON AND ADMINISTRATION OF THE HOSPITAL FOR TROPICAL DISEASES



In the fiscal year 2004 (October 2003-September 2004) the number of patients treated in the Hospital for Tropical Diseases were classified by disease, as follows:

| Diseases | No. of out-patients | No. of in-patients |
|---|---|---|
| 1. Falciparum malaria | 326 | 320 |
| 2. Vivax malaria | 398 | 324 |
| 3. Mixed falciparum and vivax malaria | 7 | 8 |
| 4. Malariae malaria | 13 | 10 |
| 5. Unidentifed infections | 36 | 32 |
| 6. Scrub typhus | 3 | - |
| 7. Typhoid | 2 | - |
| 8. Diarrhea | 132 | 11 |
| 9. Food poisoning | 37 | 3 |
| 10. Hepatitis | 812 | 21 |
| 11. Dengue hemorrhagic fever | 127 | 114 |
| 12. Leptosprirosis | 3 | 3 |
| 13. Taeniasis | 40 | - |
| 14. Hookworm | 10 | - |
| 15. Ascariasis | 2 | - |
| 16. Liver flukes | 18 | - |
| 17. Pinworm | 7 | - |
| 18. Strongyloidiasis | 15 | - |
| 19. Gnathostomiasis | 777 | 2 |
| 20. Filariasis | 3 | 2 |
| 21. Dermatitis | 2,834 | 6 |
| 22. Tuberculosis (pulmonary) | 146 | 4 |
| 23. HIV infecsions | 38 | 1 |
| 24. Hypertension | 2,223 | 35 |
| 25. Diabetes mellitus | 1,678 | 31 |
| 26. Hyperlipidemia | 1,382 | - |
| 27. Diseases of oral cavity, salivary gland and jaw | 278 | 179 |
| 28. Others | 20,039 | 536 |
| **Total** | **31,386** | **1,642** |

## OTHER SPECIAL CLINICS:

- **Dermatology clinic:** Monday-Thursday; 9.00-12.00 hr. (Assoc. Prof. Wichai Supanaranond and Dr. Jttima Dhitavat)
- **Children's clinic:** Monday-Friday ; 9.00-12.00 hr. (Assoc.Prof.Pornthep Chanthavanich, Assoc.Prof. Krisana Pengsaa , Assoc.Prof. Chukiat Sirivichayakul Dr.Keswadee Lapphra and Dr.Kriengsak Limkittikul)
- **Chest clinic:** Tuesday; 9.00-12.00 hr. (Assist.Prof. Udomsak Silachamroon
- **Gastroenterology clinic:** Tuesday ; 9.00-12.00 hr. (Prof. Polrat Wilairatana)
- **Liver clinic:** Monday; 9.00-12.00 hr. (Assoc. Prof. Wattana Leowattana, Dr.Sombat Treeprasertsuk, Dr.Wichai Ekataksin)
- **Geriatric clinic:** Tuesday; 9.00-12.00 hr. (Assoc.Prof. Srivicha Krudsood)
- **Ear, nose, throat clinic:** Tuesday; 9.00-12.00 hr. (Assoc. Prof. Yaowalark Sukthana)
- **Gnathostomiasis clinic:** Wednesday and Friday; 9.00-12.00 hr. (Assoc.Prof. Mario Riganti and Assist.Prof.Valai Bussaratid)
- **Nephrology clinic:** Monday and Wednesday; 9.00-12.00 hr. (Assist.Prof.Weerapong Phumratanaprapin and Dr.Wipa Thanachartwet)
- **Thai Traditional massage:** every day ; 8.00-20.00 hr.
- **Traditional Chinese acupuncture:** Monday-Wednesday; 9.00-11.00 hr. (Assoc. Prof. Wichai Supanaranond)

## SPECIAL LABORATORY SERVICES

| Disease/Infection | Serological test used | Specimen required | Time required (days) | Cosh per test (Baht) | Place where specimen should be sent |
|---|---|---|---|---|---|
| Alpha-fetoprotein | ELISA | Clotted blood 5 ml | 2 | 200 | Microbiology Serology & Immunology Unit via OPD |
| Anti DNA | Fluorescent | Clotted blood 5 ml | 2 | 80 | Microbiology Serology & Immunology Unit via OPD |
| Anti HAV IgM | EIA | Clotted blood 5 ml | 1 | 250 | Microbiology Serology & Immunology Unit via OPD |
| Anti HCV | EIA | Clotted blood 5 ml | 1 | 250 | Microbiology Serology & Immunology Unit via OPD |
| Anti HIV quick test | PHA + EIA | EDTA blood 2 ml | 2hr. | 300 | Microbiology Serology & Immunology Unit via OPD |
| Anti HIV | PHA + EIA | Clotted blood 2 ml | 1 | 150 | Microbiology Serology & Immunology Unit via OPD |
| Cryptococcal/Ag | Agglutination | Clotted blood 5 ml | 2 | 150 | Microbiology Serology & Immunology Unit via OPD |
| Dengue IgG & IgM | HAI | Clotted blood 5 ml | 1 | 250 | Microbiology Serology & Immunology Unit via OPD |
| *E. histolytica* Ab | PHA | Clotted blood 5 ml | 1 | 100 | Microbiology Serology & Immunology Unit via OPD |
| HBs Ag | EIA | Clotted blood 5 ml | 1 | 120 | Microbiology Serology & Immunology Unit via OPD |
| HBs Ab | EIA | Clotted blood 5 ml | 1 | 120 | Microbiology Serology & Immunology Unit via OPD |
| HBc Ab | EIA | Clotted blood 5 ml | 1 | 120 | Microbiology Serology & Immunology Unit via OPD |
| VDRL | Agglutination | Clotted blood 5 ml | 1 | 60 | Microbiology Serology & Immunology Unit via OPD |
| Leptospiral Ab | IFA | Clotted blood 5 ml | 1 | 150 | Microbiology Serology & Immunology Unit via OPD |
| Mycoplasma Ab | Agglutination | Clotted blood 5 ml | 1 | 200 | Microbiology Serology & Immunology Unit via OPD |
| *P.pseudomallei* Ab | Agglutination | Clotted blood 5 ml | 1 | 80 | Microbiology Serology & Immunology Unit via OPD |
| Rheumatoid factor | Agglutination | Clotted blood 5 ml | 1 | 100 | Microbiology Serology & Immunology Unit via OPD |
| Widal test | Agglutination | Clotted blood 5 ml | 1 | 100 | Microbiology Serology & Immunology Unit via OPD |
| Weil Felix test | Agglutination | Clotted blood 5 ml | 1 | 120 | Microbiology Serology & Immunology Unit via OPD |
| Scrub typhus Ab | IFA | Clotted blood 5 ml | 2 | 150 | Microbiology Serology & Immunology Unit via OPD |
| Murine typhus Ab | IFA | Clotted blood 5 ml | 2 | 150 | Microbiology Serology & Immunology Unit via OPD |

# SEAMEO TROPMED Regional Centre for Tropical Medicine (TROPMED/Thailand)

**FACULTY OF TROPICAL MEDICINE, MAHIDOL UNIVERSITY, BANGKOK, THAILAND**

**ASSOC. PROF. PRATAP SINGHASIVANON** Director

TROPMED/Thailand has 3 major functions namely 1) Teaching and training 2) Research and 3) Services. Activities of the 3 functions are reported according to the 5 KEY RESULTS AREAS as follows:

## KRA 1 ENHANCED PROGRAMME QUALITY AND RELEVANCE

1.1 **Post-graduate regular courses.** TROPMED/Thailand offers five post-graduate, regular courses at the international level with a total of 236 students from 49 countries.

1.2 **Undergraduate courses.**

TROPMED/Thailand also offers 2 undergraduate courses:

1) Elective programme in tropical medicine with 16 medical students from 6 countries.
2) Certificate in Nurse Assistant with 200 students.

In the year FY 2003/2004, TROPMED/Thailand had 452 students from 22 countries; among these, 299 were new enrolled students in 20 countries. 434 of these students were fee-paying attendants.

Table 1: Number of students attending the 5 regular courses

| Courses | Number | No. (Nationality) | No. of fee-paying Students | No. of Graduates |
|---|---|---|---|---|
| DTM&H 6-month course | 32 | 17 (Australia, Bangladesh, Cambodia, Ethiopia, India, Indonesia, Japan, Lao PDR, Myanmar, Philippines, Sri Lanka, Switzerland, Spain, Thailand, United Arab Emirates, United Kingdom, USA) | 29 (90.62%) | 32 (100%) |
| MCTM 1-year course | 10 | 8 (Cambodia, India, Lao PDR, Myanmar, Sri Lanka, Switzerland, Thailand, United Arab Emirates) | 7 (70%) | 10 (100%) |
| MSc (TM) | | | | |
| 1st year | 29 | 4 (Bangladesh, Japan, Nepal, Thailand) | 78 (91.76%) | 8 (9.41%) |
| 2nd year | 17 | 3 (Japan, Nepal, Thailand) | | |
| 3rd year | 16 | 2 (Thailand, Vietnam) | | |
| 4th year | 14 | 1 (Thailand) | | |
| 5th year | 6 | 2 (Thailand, Lao PDR) | | |
| 6th year | 3 | 1 (Thailand) | | |

Table 1: Number of students attending the 5 regular courses (*continued*)

| Courses | Number | No. (Nationality) | No. of fee-paying Students | No. of Graduates 2003 |
|---|---|---|---|---|
| Postgraduates PhD (TM) | | | | |
| 1st year | 12 | 2 (Bangladesh, Thailand) | 100 (95.2%) | 5 (4.76%) |
| 2nd year | 19 | 1 (Thailand) | | |
| 3rd year | 20 | 2 (Thailand, Vietnam) | | |
| 4th-9th year | 54 | 3 (Korea, Switzerland, Malaysia Thailand) | | |
| PhD (Clin.Trop.Med) | 4 | 3 (Myanmar, Japan, Thailand) | 4 (100%) | - |
| **Subtotal** | **236** | | **218 (92.37%)** | **55 (23.30%)** |
| Undergraduate Elective Programme in tropical Medicine | 16 | 6 (Austria, Canada, Japan, Malaysia, United Kingdom, USA) | 16 (100%) | 16 (100%) |
| Certificate in Nurse Assistants | 200 | 1 (Thailand) | 200 (100%) | 200 (100%) |
| **Sub Total** | **216** | | **216 (100%)** | **216 (100%)** |
| Grand Total | 452 | 22 | 434 (96.01%) | 271 (59.95%) |

1.3 **Training course/Workshop/Meeting.** Eight international training courses and 1 international meeting were convened during FY 2003/2004 with a total number of 706 participants from 38 countries.

## KRA 2 INCREASED ACCESS TO MARKET

2.1 **Active Marketing.** Thirty-seven TV series were broadcast, fifteen news items published in local newspapers, 16 radio announcements. 5 tropical diseases information leaflets were produced and distributed to the public and 92 news items were announced in the Mahidol's website.

## KRA 3 INCREASED LINKAGES

3.1 **WHO Collaborating Centre:** World Health Organization has designated the Faculty of Tropical Medicine as a WHO Collaborating Centre for Clinical Management of Malaria.

3.2 **Visitors.** Thirty-three visitors from 7 countries visited TROPMED/Thailand during FY 2003/2004.

## KRA 4 IMPROVED FINANCIAL STATUS

There were three sources of revenue for activities pertaining to the three major roles of TROPMED/Thailand: 1) Government budget, 2) Revenue from medical care fees, academic services and other activities, and 3) Research funds.

Table 2: Sources of revenue

| Sources | Amount in million Baht | Percentage Increase / Decrease |
|---|---|---|
| 1. Government budget | 122.24 | -0.71% |
| 2. Revenue from services and other activities | 94.20 | -19.48% |
| 3. Research funds from other organizations | 168.25 | +50.87% |

## KRA 5 ENHANCED QUALITY OF SEAMEO MANAGEMENT

TROPMED/Thailand has a total of 849 staff comprising 139 academic staff, 179 academic assistants and research staff, 146 administrative personnel, 125 university employees and 385 employees. The qualification and academic posts by these 139 academic staff the year under review are shown in Table 3.

### Table 3: Qualification of 139 academic staff

| Qualification | No | Percentage (%) |
|---|---|---|
| 1. PhD | 65 | 46.76 % |
| 2 . Master | 74 | 53.23 % |
| 3. Bachelor | - | - |
| **Total** | **139** | **100 %** |

The academic posts of 139 academic staff compared to those of Mahidol University are shown in Table 4.

### Table 4: Academic posts of 139 staff pf TROPMED/Thailand

| Academic Posts | Academic Posts | |
|---|---|---|
| | Holding by FTM Staff No. (%) | Holding by Mahidol Staff No. (%) |
| Professors | 5 (3.59%) | 126 (5.28%) |
| Associate Professors | 34 (24.46%) | 780 (32.78%) |
| Assistant Professors | 33 (23.74%) | 817 (34.28%) |
| Lecturers | 67 (48.20%) | 660 (27.69%) |
| **Total** | **139 (100.00%)** | **2,383 (100.00%)** |

5.1 Number of staff promoted or obtaining higher qualification

### Table 5: Number of staff promoted

| | | |
|---|---|---|
| Academic rank | : Professors | = - |
| | Associate Professors | = 2 |
| | Assistant Professors | = 2 |
| Career rank | : Higher rank | = 48 |
| Higher qualification | : Higher degree | = 8 |
| | **Total** | **= 60** |

5.2 **Number of research projects and publication.** TROPMED/Thailand staff undertaken 120 research projects with total research grants of 168.25 million Baht and 141 published research papers.

Table 7: Number of research projects and publication

| | New Project | On-going | Accomplished |
|---|---|---|---|
| Number of research projects | 23 (19.16%) | 74 (61.66%) | 23 (19.16%) |
| Number of published papers | 127 | | |

5.3 Number of staff taking study leave, attending training course and attending meetings/seminars/workshops.

Eight staff (0.41%) took study leaves for higher education. One thousand nine hundred and thirty nine staff (99.58%) attended training, meetings, seminars, and workshops in country and abroad. One staff may attend more than one training/meeting/seminar/workshop.

Table 8: Staff development through higher study, training courses, seminars/workshops.

| Category of staff development | In country | Abroad | Total |
|---|---|---|---|
| Study leave | 8 (0.46%) | 0 (0.0%) | 8 (0.41%) |
| Attending training courses<br>Seminars, meetings workshops | 1,715 (99.53%) | 224 (100%) | 1,939 (99.58%) |
| **Number of staff** | **1,723 (100%)** | **224 (100%)** | **1947 (100%)** |

5.4 Special talks / lectures

To develop and/or improve knowledge of staff, 4 lunch talks/lectures on various topics for 110 attendants, 14 CME lectures (Continuing Medical Education) including information technology were organized for 388 attendants.

5.5 Patients treated for tropical diseases

The Hospital for Tropical Diseases offers medical care services to patients suffering from tropical and other diseases. The Hospital has 250 beds with 30 medical doctors, 94 nurses and 80 nurse assistants. The total numbers of out patients treated were 30,081 and the numbers of patients admitted to the Hospital were 1,707. Routine and special laboratory services for diagnosis of tropical infections were also provided.

5.6 Improved infrastructure

1. Rajanagarindra Tropical Diseases International Centre (RTIC) is a center for conducting field research on tropical diseases located at Suan Phung district, Rachaburi Province.
2. Tropical Diseases Research Centre Kanchanaburi is one of the Faculty's centers for conducting tropical disease research and a field training center for students located at the Kanchanaburi campus of Mahidol University.
3. Eight computers were installed in the computer center for training and studying courses of the Faculty of Tropical Medicine.
4. During the FY 2003/2004, renovations of the Faculty were conducted, including the Hospital for Tropical Diseases, administration building, and Data Management Unit and VaccineTrial Center.
5. Since an International Guest House with 66 rooms has been opened, 30 students/guests/visitors from 16 countries were served in FY 2003/2004.

# The Asian Centre of International Parasite Control (ACIPAC)

**Office Telephone:** 66 (0) 2354-9100 ext. 1338, 1339; **Fax:** 66 (0) 2643-5616; **E-mail:** tmacipac@diamond.mahidol.ac.th

**PROF. SOMEI KOJIMA** Chief Advisor

ACIPAC organized a six-week training course on School-based Malaria and STH Control for Program Managers during 20 June to 30 July 2004. 29 participants attended the course, from Cambodia, Lao PDR, Myanmar, Thailand, Vietnam, Kenya, Ghana and Timor L'este. A Small-scale Pilot Project on school-based STH control was conducted in Cambodia, Lao PDR, Myanmar and Vietnam with support from ACIPAC. In January 27-28, 2005, a seminar was organized to summarize the project outcomes. 2004 was the final year of the project; a terminal evaluation was carried out and the conclusion was attached as follows:

## EVALUATION OF THE ACIPAC PROJECT

Prior to the end of the ACIPAC project, JICA dispatched a terminal evaluation team from 7 November to 13 November 2004 to evaluate the implementation and achievements of the Project. The team headed by Dr. Akira Hashizume analyzed and discussed jointly with Thai authorities the achievements of the Project in terms of relevance, effectiveness, efficacy, impact, sustainability and the future directions. Results of their careful studies and discussions are summarized as follows. Details of the Joint Evaluation Report will be attached separately. The following are selected from the Minutes of Meeting between the Japanese Evaluation Team and the Authorities Concerned of the Government of the Kingdom of Thailand on the ACIPAC Project.

### (1) Conclusion:

The Project has significantly realized four different outputs and achieved the Project Purpose. However, some major tasks remain unfinished, reflecting more and detailed needs expressed by those concerned. One of the major tasks is the provision of a training course to meet different types of needs for human resource development. Another major responsibility is to strengthen networking among partner countries and donors, as well. Networking of the partner countries specifically for mainstreaming the school-based approach in the policy direction is necessary. Furthermore, information sharing and partnership for human resource development among donors and partner countries are necessary.

The possibility of the subsequent cooperation of JICA should be considered, because ACIPAC is likely to have more tasks to meet a variety of needs expressed by those concerned. Mahidol University still needs support for some of the areas in the training course and coordination of tasks among partner countries and donors.

### (2) Recommendations:

1) Summary and dissemination of the SSPP's experiences in partner countries: ACIPAC should confirm the achievement and implementation process and evaluate the SSPP and summarize them as case study or reference book to enable those interested in school health and parasite control to utilize the experience of the SSPP. 2) Further effort to improve the curriculum, content, and administration of the international training course to meet the wide ranging needs: There were many suggestions from ex-trainees, the partner countries, and donors to improve the course in order to meet the wide ranging needs, such as organizing the course separately for those with different levels of knowledge and skill, inviting trainees from other countries, or organizing in country training. If the training course is to be continued, such further efforts should be made to meet a variety of requests. 3) Establishment of a system to sustain and strengthen the human/information network: Staff in charge of the human/information networking should be assigned to sustain the activities. The Japanese experts should transfer necessary knowledge and skills to the newly assigned staff. In addition, IT committee should be reactivated to identify what should be done. Follow-up activities in each country should be explored as well. 4) Implementation of every measure to increase sustainability: Every measure to increase sustainability should be explored by approaching a variety of funding and technical agencies (e.g. Asian Development Bank, WHO, UNICEF, SEAMEO TROPMED Network).

### (3) Lessons learnt

1) Intensive communication and mutual understanding among stakeholders: Intensive communication and resulting mutual understanding among stakeholders, especially JICA headquarter, resident offices, the counterpart authorities, and the experts concerned, at the planning and implementation stage, should be done in a region-wide technical cooperation project. A lack of such communication and understanding also could reduce the sense of ownership of the counterpart organizations. 2). Combination of the experiences of the Japanese and other countries for a particular approach with adequate adjustment: The combination of the Japanese and Thai experiences on school-based parasite control was more useful than application of the Japanese experience alone to be introduced to the partner countries. However, at the same time, the approach needs to be adjusted carefully to the context of each country. 3) Appropriate selection of the method to disseminate information to different target groups: As mentioned earlier, ACIPAC has made an effort to disseminate information through the information network, but encountered problems in reaching target groups, such as ex-trainees. Appropriate methods should be considered and implemented by considering the situations of the target groups. 4) Introduction of an appropriate process of selecting candidates for the training course: Proper criteria and system for selecting candidates should be informed to the organizations concerned from the initial stage of the project. 5) Expansion of a region-wide technical cooperation project to a bilateral scheme: ACIPAC covered a large scope of activities, including coordination between the Ministry of Education and the Ministry of Health, the formulation of a national task force and policy. It could lead to the request of the Lao side for dispatch of a Japanese expert on school health. This experience of leading to bilateral cooperation based on the output of a region-wide technical cooperation project should be shared and utilized for other similar projects.

To respond to the recommendation described here, ACIPAC has drafted several possible courses for international and in-country training so as to reflect on a variety of needs in human resource development. In addition, a new committee has been assigned towards future establishment of human/information networking. The implementation of possible training courses and how to establish networking in this region will be main topics for future activities in the ACIPAC Final Symposium to be held on 27-28 January 2005.

# Office of the Dean

**Office Telephone:** 0 2354 9100-19 ext. 1326, 1328; **Fax:** 0 2354 9139

**Mrs. Vorapan Singhsilarak**
Secretary of the Faculty
B.A.

The Office of the Dean is a support unit facilitating the major tasks of the Faculty, such as teaching, research, academic services, and hospital services, to meet the goals of the Faculty. The Office of the Dean is conducted under the authority and supervision of the Secretary of the Faculty and Deputy Deans with related duties. It can be differentiated into 10 major units, i.e., Administration and General Affairs Unit, Personnel Unit, Policy and Planning Unit, Financial and Procurement Unit, Educational Affairs Unit, Information Technology Unit, Educational Technbology Unit, International Relations Unit, Area and Maintenance Unit, and Research and Academic Affairs Unit.

## Vision for the Office of the Dean
## " PLEASED TO BE OF SERVICE "

## ORGANIZATION CHART

**OFFICE OF THE DEAN**

- Administration Unit & General Affairs
- Educational Affairs Unit
- Financial and Procurement Unit
- Research and Academic Affairs Unit
- Policy and Planning Unit
- Personnel Unit
- Educational Technology Unit
- Information Technology Unit
- International Relations Unit
- Building and Manitenance Unit
- Vaccine Trial Centre and Data Management Unit
- Central Equipment Unit
- The Wellcome-Mahidol-Oxford Tropical Medicine Research Unit
- Laboratory Animal Unit

# Training Programs

## FACULTY OF TROPICAL MEDICINE, MAHIDOL UNIVERSITY

During January – December 2004

### 1) 26 January – 20 February 2004

Special Training on Tropical Disease Management for Japanese physicians

| | |
|---|---|
| Japan | 2 |

### 2) 1 – 31 March 2004

Pre-course for Thai Government Fellows

| | |
|---|---|
| Lao P.D.R. | 1 |
| Cambodia | 1 |
| Sri Lanka | 1 |

### 3) 5 July – 27 August 2004

International Training Course in Partnership Building on Healthy Borders

| | |
|---|---|
| Bangladesh | 2 |
| Cambodia | 2 |
| Myanmar | 1 |
| Vietnam | 4 |
| Lao P.D.R. | 2 |
| Thailand | 2 |

### 4) 4 – 13 August 2004

WHO Training program on Laboratory Diagnosis of Malaria

| | |
|---|---|
| DRP Korea | 3 |

### 5) 16 – 27 August 2004

Malaria Training Program for Medical doctors and Public Health Personnel from Taiwan's CDC

| | |
|---|---|
| Taiwan | 15 |

### 6) 13 – 24 September 2004

The International Training Course on Management of Malaria 2004

| | |
|---|---|
| Guinea | 1 |
| Germany | 1 |
| Timor | 2 |
| Myanmar | 2 |
| Zimbabwe | 2 |
| Thailand | 1 |

### 7) 11 October – 19 November 2004

Training in Immunological Techniques on Rapid Diagnostic Test of Malaria

| | |
|---|---|
| Myanmar | 1 |

### 8) 14 – 20 November 2004

Workshop on Parasite Control for Latin America and the Caribbean

| | |
|---|---|
| Japan | 2 |
| Argentina | 1 |
| Brazil | 2 |
| Colombia | 1 |
| Costa Rica | 2 |
| Ecuador | 1 |
| El Salvador | 1 |
| Jamaica | 1 |
| Honduras | 1 |
| Mexico | 2 |
| Nicaragua | 1 |
| Panama | 1 |
| Paraguay | 1 |
| Uruguay | 2 |

### 9) 7 – 27 December 2004

Training in In Vivo Drug Sensitivity Testing of Antimalarials, Data Analysis

| | |
|---|---|
| Myanmar | 1 |

# MOU/Agreement

1. Southeast Asian Ministers of Education Organization (SEAMEO) and the Government of Thailand
2. Freie Universitat at Berlin, Germany
3. Universite Pierre et Marie Curie, France
4. The Swiss Tropical Institute, Basel, Switzerland
5. University of Tsukuba, Japan
6. Liverpool School of Tropical Medicine, United Kingdom
7. Canadian Food Inspection Agency, Government of Canada, Saskatoon, Canada
8. Nagasaki University, Japan
9. Japan International Cooperation Agency (JICA), Japan
10. Faculty of Social Science and Humanities, MU, Department of Communicable Disease Control, Ministry of Public Health
11. Ewha Woman's University, South Korea
12. Nuffield Department of Medicine, University of Oxford, London, United Kingdom
13. University of Leicester, United Kingdom
14. University of Innsbruck, Austria
15. Department of Medical Sciences, Ministry of Public Health
16. Chiangrai Regional Hospital, Ministry of Public Health
17. Japan International Corporation of Welfare Services (JICWELS), Japan

# Visitors

| Name | Country |
|---|---|
| 1. Dr. Robert Bos | Switzerland |
| 2. Prof. Richard Kay | Hong Kong |
| 3. Dr. Kimiya Sato | Japan |
| 4. Prof. Gary Brittenham | USA |
| 5. Mr. Kei Yokota | Japan |
| 6. Ms. Yuki Okada | Japan |
| 7. Mr. Taku Uchiyama | Japan |
| 8. Ms. Makiko Mitsunami | Japan |
| 9. Ms. Yuki Imaizumi | Japan |
| 10. Mr. Yoshihiro Kurokawa | Japan |
| 11. Mr. Ryosuke Okuyama | Japan |
| 12. Mr. Sho Sawada | Japan |
| 13. Mr. Shinya Miura | Japan |
| 14. Ms. Yoshiko Nakano | Japan |

| Name | Country |
|---|---|
| 15.Mr. Kenji Ohshima | Japan |
| 16. Mr. Masatha Thaonpom | Thailand |
| 17. Mr. Jakrapan Jirasiritham | Thailand |
| 18. Mr. Sornwichate Rattanachaiwong | Thailand |
| 19. Ms. Tanya Leelasiriwong | Thailand |
| 20. Ms. Unyaporn Suthutvoravut | Thailand |
| 21. Mr. Wuttichai Thaisamarn | Thailand |
| 22. Ms. Sarocha Wuthiputhanan | Thailand |
| 23. Ms. Pinkate Rosmim | Thailand |
| 24. Mr. Thepkhachai Kengkijkosol | Thailand |
| 25. Mr. Norasak Suvachittanont | Thailand |
| 26. Mr. Worawat Siripoon | Thailand |
| 27. Dr. Rebecca Traub | Australia |
| 28. Prof. David Warrell | UK |

| Name | Country |
|---|---|
| 29. Dr. Richard K. Hanes | Hong Kong |
| 30. Dr. Syahril Pasaribu | Indonesia |
| 31. Dr. Harwinta F. Eyanoer | Indonesia |
| 32. Prof. Coll Seck | Senegal |
| 33. Dr. Banda | Senegal |
| 34. Dr. Tuescher | Senegal |
| 35. Dr. Kimiya Sato | Japan |
| 36. 12 Vietnamese | Vietnam |
| 37. Mr. Samba Laobe Dieng | Senegal |
| 38. Mr. Ibrahima Mbodj | Senegal |
| 39. Mr. Swangwat Srihakote | Thailand |
| 40. Mr. Keven Lunney | USA |
| 41. H.E. Pehin Dato Haji Abd Aziz Umar | Brunei |
| 42. Datin Paduka Hajah Zaharah Binti Haji Idris | Brunei |
| 43. Sheikh Haji Adnan bin Sheikh Mohamad | Brunei |
| 44. Dyg Apsah binti Haji Abd Majid | Brunei |
| 45. Dr. Omar bin Haji Khalid | Brunei |
| 46. Haji Abd Salam bin POKPS DP Haji Hashim | Brunei |

| Name | Country |
|---|---|
| 47.Dyg Hajah Aming binti Haji Wasli | Brunei |
| 48. Prof. Tom van der Poll | Netherlands |
| 49. Prof. Cynthia Haq | USA |
| 50. Dr. Chris Hentschel | Switzerland |
| 51. Dr. Mark Walport | UK |
| 52. Dr. Sohaila Rastan | UK |
| 53. Prof. James Whitworth | UK |
| 54. Dr. Michael Chew | UK |
| 55. Mr. Shinjiro Nozaki<br>Japan International Corporation of Welfare Services | |
| 56. Mr. Hajime Fukunaga<br>International University of Health and Welfare, Japan | |
| 57. 9 Japanese students<br>International University of Health and Welfare, Japan | |

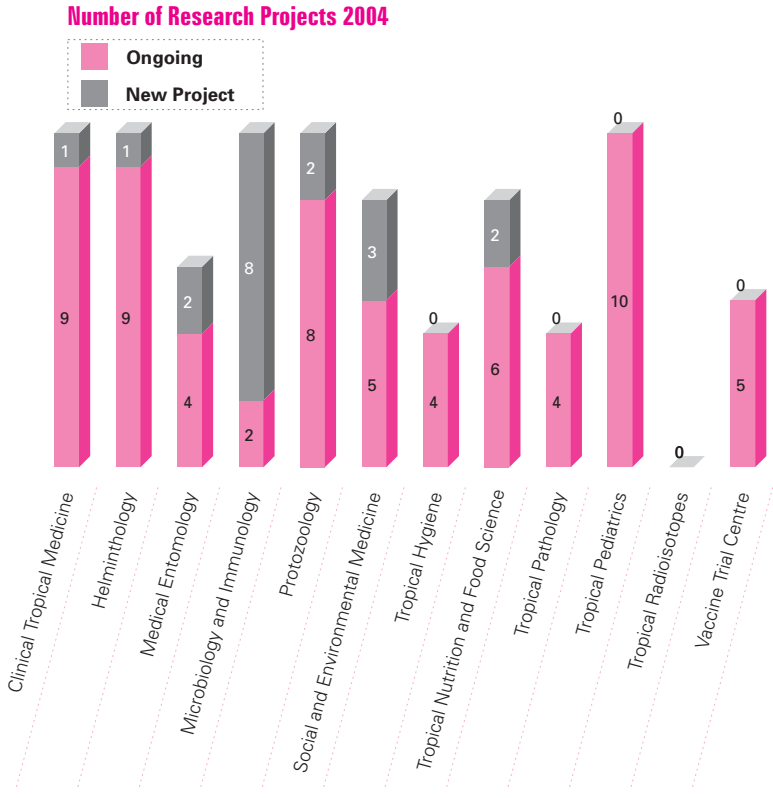
## INTERNSHIP

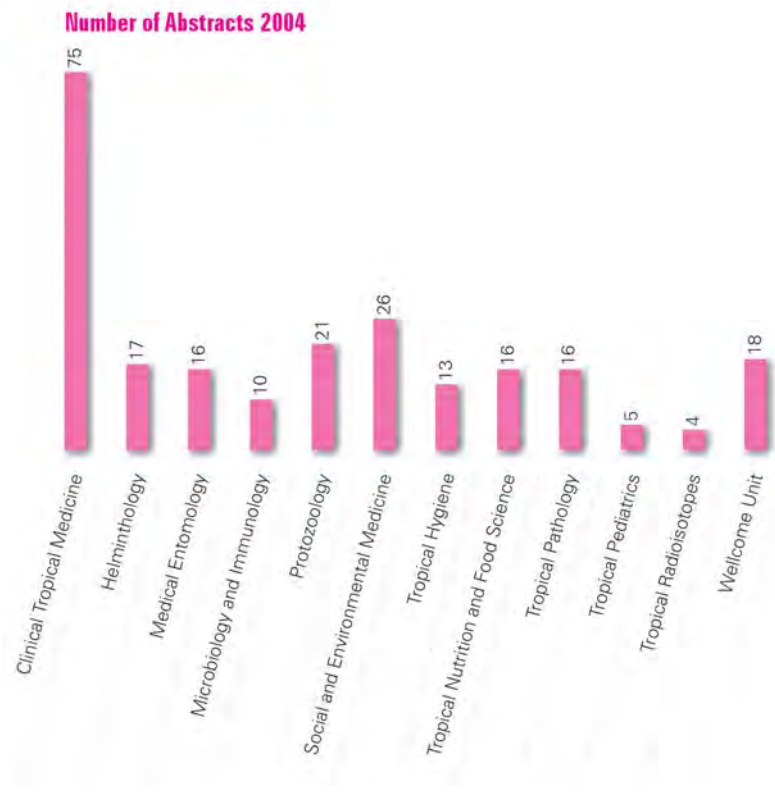
| | |
|---|---|
| 52. Dr. Jan Bornert | Germany |
| 53. Ms. Kimberly Brown | Canada |

## DELEGATES ATTENDED ELECTIVE PROGRAMME IN TROPICAL MEDICINE

| Name | Institute | Country | Period |
|---|---|---|---|
| 1. Mrs.Naomi Mraz | University of Minnesota | USA | 26 Jan. – 20 Feb.04 |
| 2. Mr.Stephen Foley | University of Southern California | USA | 26 Jan. – 20 Feb.04 |
| 3. Mrs.Catharine Keay | University of Washington | USA | 2 – 27 Feb.04 |
| 4. Mr.Masafumi Horie | University of Tokyo | Japan | 2 – 27 Feb.04 |
| 5. Mr.Hiromichi Tamaki | University of Tokyo | Japan | 2 – 27 Feb.04 |
| 6. Mr.Kei Yokota | Jichi Medical School | Japan | 12 March 2004 |
| 8. Dr. Zakuan Deris | University Sains Malaysia | Malaysia | 3 – 28 May 2004 |
| 9. Ms. Mellisa Fyhn | University of Calgary | Canada | 14 June – 9 July 04 |
| 10. Ms. Parneet Cheema | University of Calgary | Canada | 14 June – 9 July 04 |
| 11. Ms. Tomoka Gomibuchi | Tsukuba University | Japan | 18 – 23 Aug. 04 |
| 12. Ms. Zhuxi Wang | Tsukuba University | Japan | 18 – 23 Aug. 04 |
| 13. Mr. Tsutomu Shioda | Tsukuba University | Japan | 18 – 23 Aug. 04 |
| 14. Ms. Eri Mizuno | Tsukuba University | Japan | 18 – 23 Aug. 04 |
| 15. Mr. Tatsuhiko Ogawa | Tsukuba University | Japan | 18 – 23 Aug. 04 |
| 16. Ms. Lina Inagaki | Tsukuba University | Japan | 18 – 23 Aug. 04 |
| 17. Mr. Isao Muraki | Tsukuba University | Japan | 18 – 23 Aug. 04 |
| 18. Ms. Yoko Uchikawa | Tsukuba University | Japan | 18 – 23 Aug. 04 |
| 19. Ms. Natsuki Kawashima | Tsukuba University | Japan | 18 – 23 Aug. 04 |
| 20. Dr. Alan Reid | | Australia | 1 Sept. – 30 Oct. 04 |
| 21. Mr. Christoph Moser | University of Vienna | Austria | 1 – 30 Sept. 04 |
| 22. Ms. Alexandra Hutter | University of Vienna | Austria | 1 – 30 Sept. 04 |
| 23. Ms. Gabriele Fink | University of Graz | Austria | 1 – 30 Sept. 04 |
| 24. Ms. Angelika Wagner | University of Graz | Austria | 1 – 30 Sept. 04 |
| 25. Ms. Julie Waack | University of Innsbruck | Austria | 1 – 30 Sept. 04 |
| 26. Ms. Catherine Sondermann | University of Innsbruck | Austria | 1 – 30 Sept. 04 |
| 27. Ms. Masami Morimoto | Oita University | Japan | 1 – 10 Sept. 04 |
| 28. Ms. Tomoko Ide | Oita University | Japan | 1 – 10 Sept. 04 |
| 29. Ms. Sarah Borge | University of Minnesota | USA | 15 Nov. – 10 Dec.04 |
| 30. Mr. Daniel Miller | University of Minnesota | USA | 15 Nov. – 10 Dec.04 |
| 31. Dr. Takehiko Sekine | Medical & Dental University | Japan | 15 Nov. – 10 Dec.04 |
| 32. Dr. Shigeki Hanafusa | Tokyo Woman's Medical University | Japan | 7 Dec.04 – 21 Jan.05 |

# Summary of Number of Research Projects and Abstracts 2004



## ONGOING RESEARCH PROJECTS OF THE FACULTY OF TROPICAL MEDICINE IN 2004

(Fiscal Year 2004)

| No. | Research Title | Grant | Principal Investigator |
|---|---|---|---|
| **Department of Clinical Tropical Medicine** | | | |
| 1 | A multicenter, randomized, double-blind, phase II study to evaluate the safety, tolerance and efficacy of multiple doses of SCH 56592 versus fluconazole in the treatment of oropharyngeal candidiasis (OPC) in HIV-positive patients | Schering Plough Research Institute | Assoc. Prof. Punnee Pitisuttithum |
| 2 | Open-label, treatment protocol for the safety and efficacy of SCH 56592 (Oral Suspension) in the treatment of invasive fungal infections | Schering Plough Research Institute | Assoc. Prof. Punnee Pitisuttithum |
| 3 | Safety and therapeutic effects of Jin Huang Chinese Medicine in uncomplicated HIV-1 patients | Huatai Pharmacy, Co., Ltd. | Assoc. Prof. Punnee Pitisuttithum |
| 4 | Observational probe study of *in vitro* immune response parameters to candidate HIV-1 vaccine antigens among subject from Thailand | MERCK and Co., Inc | Assoc. Prof. Punnee Pitisuttithum |
| 5 | Efficacy and tolerability of ivermectin on gnathostomiasis Research Programme | Thailand-Tropical Diseases | Assist. Prof. Valai Bussaratid |
| 6 | Research and development for Thai people living at Thai-Myanmar border to free from tropical diseases | Government Budget | Prof. Sornchai Looareesuwan |
| 7 | Research and development on drugs and diagnostic tools for diagnosis and treatment of tropical diseases in Thailand | Government Budget | Prof. Sornchai Looareesuwan |
| 8 | Development of field methods and investigators of the molecular basis of Sulfonamide resistance in *Plasmodium vivax* | Wellcome Trust of Great Britain | Assist. Prof. Mallika Imwong |
| 9 | Novel point mutations in the dihydrofolate reductase gene of *Plasmodium vivax*: evidence for sequential selection by drug presure | Wellcome Trust of Great Britain | Assist. Prof. Mallika Imwong |
| *10 | Liver megaproject Phase I: from basic research to education science and applied technology in clinical study | National Science and Technology Development Agency | Dr.Wichai Ekataksin |
| **Department of Helminthology** | | | |
| 11 | Monoclonal antibody-based competitive ELISA and indirect ELISA for immunodiagnosis of trichinosis | Mahidol University | Mrs. Supaporn Nuamtanong |
| 12 | *Angiostrongylus cantonensis*: S-Adenosylmethionine decarboxylase | Government Budget | Mrs. Supaporn Nuamtanong |
| 13 | Comparison of biochemical extract preparations of *Cysticercus cellulosae* by SDS - polyacrylamide gel electrophoresis and immunoblot technique | Mahidol University | Assoc. Prof. Paron Dekumyoy |
| 14 | Experimental infection of freshwater fish in Thailand with the infective stage of *Angiostrongylus cantonensis* | Mahidol University | Assist. Prof. Chalit Komalamisra |
| 15 | *Toxocara canis* larval antigens for serodiagnosis of human toxocariasis | Mahidol University | Assoc. Prof. Wanna Maipanich |
| 16 | Comparative studies on surface ultrastructure of adult worm of *Paragonimus* sp. in Thailand | Mahidol University | Assist. Prof. Sanan Yaemput |
| 17 | Studies on the efficacy of Thai traditional herbal medicines in the treatment of opisthorchiasis in hamsters | Mahidol University | Assist. Prof. Panyawut Hiranyachattada |
| 18 | Research and development of the intergrated project on chemotherapy and control of malaria and parasitic infections | Government Budget | Assoc. Prof. Jitra Waikagul |

| No. | Research Title | Grant | Principal Investigator |
|---|---|---|---|
| **Department of Helminthology** (Continued) | | | |
| 19 | Research and development of an application to purify *Bithynia* snail antigen in serodiagnosis of opisthorchiasis | Government Budget | Assoc. Prof. Jitra Waikagul |
| *20 | Epidemiology of strongyloidiasis and and treatment with ivermectin | Government Budget | Assoc. Prof. Ponganant Nontasut |
| **Department of Medical Entomology** | | | |
| 21 | Specificity of the synthetic primers from sequencing DNA fragments of *Anopheles minimus* | Faculty of Tropical Medicine | Assoc. Prof. Narumon Komalamisra |
| 22 | Mosquito repellent from medicinal plants | Mahidol University | Assoc. Prof. Narumon Komalamisra |
| 23 | Effect of heavy metals (Pb2+, Cd2+) on enzymes of *Culex quinquefasciatus* larvae | Mahidol University | Mrs. Raweewan Srisawat |
| 24 | Study on fauna of medically important vectors at Kanchanaburi Campus Sai Yok District, Kanchanaburi Province | Mahidol University | Assoc. Prof. Somjai Leemingsawat |
| *25 | DNA Bank of Mosquito Vectors of Thailand | Government Budget | Assoc. Prof. Chamnarn Apiwathnasorn |
| *26 | Development of mosquito repellent formulation of mixture of volatile oils from *Artemisia annua* and *Citrus hystrix* DC. | Tropical Disease Trust | Mrs. Keawmala Palakul |
| **Department of Microbiology and Immunology** | | | |
| 27 | Analysis of sequence polymorphism of T-cell epitope regions, Th2R and Th3R on *Plasmodium falciparum* circumsporozoite proteins in Thai isolates | The Thailand Research Fund (Royal Golden Jubilee) | Prof. Srisin Khusmith |
| 28 | Cytokine gene polymorphism in severe malaria | The Thailand Research Fund (Royal Golden Jubilee) | Prof. Srisin Khusmith |
| 29 | Relationship between cytokine gene polymorphism and severity of falciparum malaria | The Thailand Research Fund | Prof. Srisin Khusmith |
| *30 | Polymophism of Pf EMP1 extracellulae domain in Thai isolates causes severe malaria uncomplicated *P. falciparum* malaria | The Thailand Research Fund (Royal Golden Jubilee) | Prof. Srisin Khusmith |
| *31 | Chemokine gene polymorphism and their susecptibility to tuberculoses | 1. The Thailand Research Fund (Royal Golden Jubilee)<br>2. Commission on Higher Education | Prof. Srisin Khusmith |
| 32 | Typing of *Entamoeba histolytica* isolates obtained from Southeast Asian countries | Japanese Health Sciences Foundation (JHSF) | Assoc. Prof. Nitaya Thammapalerd |
| *33 | HLA typing of amoebiasis | Japanese Health Sciences Foundation (JHSF) | Assoc. Prof. Nitaya Thammapalerd |
| 34 | Study of the active site between the three-dimensional tructure of R-PE-Mab complex | The Thailand Research Fund (Royal Golden Jubilee) | Assoc. Prof. Nitaya Thammapalerd |
| 35 | Development of strategies for serovar identification of *Leptospira* sp. based on specific gene sequences within rfb locus | Thailand-Tropical Diseases Research Programmes | Assist. Prof. Thareerat Kalambaheti |
| *36 | Development of dipstick assay technology during *Plasmodium falciparum* as model | Mahidol University | Miss Jarinee Panitchakorn |

| No. | Research Title | Grant | Principal Investigator |
|---|---|---|---|
| **Department of Protozoology** | | | |
| 37 | Comparison of *Toxoplasma gondii* antibody detection isolation and characterization of DNA helicase from *Plasmodium falciparum* | Thanad-Molee Choman Foundation | Assist. Prof. Varaporn Suphadtanapongs |
| 38 | Detection of malaria parasites in after-drug treatment patients by using QBC method | Government Budget | Assist. Prof. Varaporn Suphadtanapongs |
| 39 | Established Thai medicinal plants for treatment of coccidiosis in pig poultry and cow | Commission on Higher Education | Assist. Prof. Chutatip Siripanth |
| 40 | Established double antibody ELISA method for detection of pathogenic protozoal antigens in the fices | National Science and Technology Development Agency | Assist. Prof. Chutatip Siripanth |
| 41 | Isolation and characterization of DNA topoisomerase I from *Trichomonas vaginalis* | Mahidol University | Assoc. Prof. Porntip Petmitr |
| 42 | Purification and characterization of DNA polymerase B of *Plasmodium falciparum* and its role in base excision repair | Thailand-Tropical Diseases Research Programmes | Assoc. Prof. Porntip Petmitr |
| *43 | Studies on virulent and drug resistant genes of malarial parasites from infected patients for development of molecular test kits | Commission on Higher Education | Assoc. Prof. Porntip Petmitr |
| 44 | Ultrastructure effects on *Toxoplasma gondii* tachyzoites after pyrimethamine and artemisinin derivative administration in animal model | The Thailand Research Fund (Royal Golden Jubilee) | Assoc. Prof. Yaowalark Sukthana |
| 45 | Dog and cat parasitic zoonoses | Tropical Disease Trust | Assoc. Prof. Yaowalark Sukthana |
| *46 | Zoonotic canine giardiasis in temple-related communities in Bangkok, Thailand | Australian Research Council | Assoc. Prof. Yaowalark Sukthana |
| **Department of Social and Environmental Medicine** | | | |
| 47 | A phase III trial of Aventis Pasteur live recombinant ALVAC-HIV (vCP 1521) priming with VaxGen gp120 B/E (AIDSVAX™ B/E) Boosting in HIV-uninfected Thai-Adults | The Henry M. Jackson Foundation for the Advancement of Military Medicine, Inc. | Dr. Supachai Reukngam (Prof. Dwip Kitayaporn) |
| *48 | Intergrated studies of human and animal heptospirosis in endemic areas of Nakhon Ratchasima, Thailand | Government Budget | Assoc. Prof. Wijitr Fungladda |
| *49 | Collaborative study to evaluated operational programme of insecticide treated bednets for malaria control in Thailand | WHO | Assoc. Prof. Piyarat Butraporn |
| *50 | Factors associating with completion and default among DOTS and self-administered therapy (SAT) for treatment of TB | WHO | Assoc. Prof. Kamolnetr Okanurak |
| 51 | Rapid detection of the rifampicin resistant *M. tuberculosis* from indoor air | Thailand-Tropical Diseases Research Programmes | Assist. Prof. Pongrama Ramasoota |
| 52 | Development of serovar specific diagnostic test using phage antibody technique | The Thailand Research Fund | Assist. Prof. Pongrama Ramasoota |
| 53 | Early detection of quinolone resistant *M. tuberculosis* from Thailand | Thailand-Tropical Diseases Research Programmes | Assist. Prof. Pongrama Ramasoota |
| 54 | Epitope mapping of monoclonal specific to *Burkholderia pseudomallei* using phage display technique | The Thailand Research Fund | Assist. Prof. Pongrama Ramasoota |

| No. | Research Title | Grant | Principal Investigator |
|---|---|---|---|
| **Department of Tropical Hygiene** | | | |
| 55 | Epidemiology and drug sensitivity of Enterobacteriaceae in a rural community near Thai-Myanmar border in Suan Phung, Ratchaburi Province 2000-2002 | Tropical Hygiene | Assist. Prof. Kasinee Buchachart |
| 56 | Study on the ecology of anopheline larvae in malaria endemic area | | Mr. Supalarp Puangsa-art |
| 57 | A survey of metacerariae in fresh-water fishes in small reservoirs in Suanphung, Ratchaburi Province | | Mr. Nipon Thanyavanich |
| 58 | Application of GIS in monitoring multi-drug resistant malaria in Greater Mekong Subregion of Southeast Asia(II) | SEAMEO TROPMED and EC-Malaria | Assoc. Prof. Pratap Singhasivanon |
| **Department of Nutrition and Food Sciences** | | | |
| 59 | Food and health relationship in Asian population | Palm oil Research Institute of Malaysia | Assoc. Prof. Supranee Changbumrung |
| 60 | Development of food and medicinal plants | Government Budget | Assoc. Prof. Supranee Changbumrung |
| 61 | Medicinal plants for treatment of hookworm | Government Budget | Assoc. Prof. Supranee Changbumrung |
| 62 | Medicinal plants against malaria | Government Budget | Assoc. Prof. Supranee Changbumrung |
| 63 | Identification of gene alterations in breast cancer | BIOTEC | Assoc. Prof. Songsak Petmitr |
| *64 | Determination of gene mutation in *hMSH2* and *hMSH6* in colon cancer | Government Budget | Assoc. Prof. Songsak Petmitr |
| 65 | Detection of serum alpha-2-macroglobulin and gene mutation in Thai obese subjects | Mahidol University | Assoc. Prof. Rungsunn Tungrongchitr |
| *66 | Detection of methylenetetrahydrofolate reductase (MTHFR C677T) polymorphism effect to hyperhomocysteinemia in Thai obese subjects: cardiovascular risk factors | Government Budget | Assoc. Prof. Rungsunn Tungrongchitr |
| **Department of Tropical Pathology** | | | |
| 67 | Pathology and immunohistochemistry of liver in AIDS: a necropsy study | Mahidol University | Assoc. Prof. Parnpen Viriyavejakul |
| 68 | Causes of diarrhea in HIV/AIDS patients | Mahidol University | Assoc. Prof. Parnpen Viriyavejakul |
| 69 | The effects of *Plasmodium falciparum*-induced cellular responses on activation of endothelial cells | Mahidol University | Assoc. Prof. Yaowapa Maneerat |
| 70 | Role of nitric oxcide in vascular pathologic changes in atherosclerosis: *in vitro* study | The Thailand Research Fund | Assoc. Prof. Yaowapa Maneerat |
| **Department of Tropical Pediatrics** | | | |
| 71 | Safety and immunogenicity of tetravalent dengue vaccine formulations in Thai adult volunteers: evaluation of three-year persistence | Aventis Pasteur (France) | Assoc. Prof. Pornthep Chanthavanich |
| 72 | Immunogenicity and adverse reaction of liquid form of Japanese encephalitis vaccine (Beijing strain) in healthy Thai children | Government Pharmaceutical Organization, Thailand | Assoc. Prof. Pornthep Chanthavanich |

| No. | Research Title | Grant | Principal Investigator |
|---|---|---|---|
| **Department of Tropical Pediatrics** (Continued) | | | |
| 73 | Follow up of Thai school children immunized with live attenuated tetravalent dengue vaccine 3 to 8 years ago: current immunity response and history of serious medical events since vaccination (EPI 10) | Aventis Pasteur (France) | Assoc. Prof. Pornthep Chanthavanich |
| 74 | Health problems, knowledge, attitudes and practices of children in Saiyok District, Kanchanaburi Province | Mahidol University | Assoc. Prof. Pornthep Chanthavanich |
| 75 | Early immune response to multi-sites intramuscular injection of purified Vero cell rabies vaccine (PVRN) for rabies post-exposure treatment (RAB 24) | Aventis Pasteur (France) | Assoc. Prof. Pornthep Chanthavanich |
| 76 | Dengue antibodies in Thai infants: age-specific seroprevalence and kinetics of transplacentally transferred dengue antibodies (EPI 11) | Aventis Pasteur (France) | Assoc. Prof. Krisana Pengsaa |
| 77 | Clinical efficacy and pharmacokinetics of suppositoried artesunate combined with mefloquine in the treatment of uncomplicated childhood falciparum malaria | Department of Tropical Pediatrics | Assoc. Prof. Chukiat Sirivichayakul |
| 78 | A comparative study of the efficacy and ease of administering salbutamol delivered from conventional meter dose inhalers and easyhaler in asthmatic Thai children | Mahidol University | Dr. Wimol Nganthavee |
| 79 | Prevalence and risk factors of atopic diseases in rural children in Saiyok District, Kanchanaburi Province | Mahidol University | Dr. Wimol Nganthavee |
| 80 | A phase II, pilot, randomized, open-label, single-center study to evaluate immunogenicity and safety after PCECV rabies vaccine (Rabipur®) administered concomitantly with Japanesse encephalitis vaccine as a pre-exposure regimen in 12 to 18 month old toddlers in Thailand | Chiron Vaccines, Co., Ltd. | Prof. Arunee Sabchareon |
| **Vaccine Trial Centre** | | | |
| 81 | Development of new vaccines against cholera due to *Vibro cholerae* 0139 (Part III) | WHO | Assoc. Prof. Punnee Pitisuttithum |
| 82 | A phase I/II trial to evaluation the safety and immunogenicity of AIDSVAX ™ B/E vaccine in Bangkok, Thailand | VAXGEN Co, Ltd. | Assoc. Prof. Punnee Pitisuttithum |
| 83 | A phase III trial to determine the efficacy of AIDSVAX™ B/E Vaccine in intravenous drug users in Bangkok, Thailand | AIDSVAX | Bangkok AIDS Vaccine Evaluation Group (Assoc. Prof. Punnee Pitisuttithum) |
| 84 | Phase I/II trial of Pasteur Merieux Connaught (PMC) live recombinant ALVAC-HIV (VCP 1521) Priming with Vaxgen gp 120 B/E (AIDVAXTM B/E) Boost in Thai HIV-Seronegative adults | Walter Reed Army Institute of Research | Assoc. Prof. Punnee Pitisuttithum |
| 85 | A phase III trial of Aventis Pasteur live recombinant ALVAC-HIV (VCP1521) priming with Vaxgen gp 120 B/E (AIDSVAX B/E) boosting in HIV-uninfected Thai adults | Walter Reed Army Institute of Research | Dr. Supachai Rueknggam (Assoc. Prof. Punnee Pitisuttithum) |

**** New project***

# TROPMED Publications 2004


1. Ahsan G, Ahmed J, Singhasivanon P, Kaewkungwal J, Okanurak K, Suwannapong N, Akarasewi P, Majid MA, Begum V, Belayetali K. Gender difference in treatment seeking behaviors of tuberculosis cases in rural communities of Bangladesh. *Southeast Asian J Trop Med Public Health* 2004; 35(1):126-35.
2. Anantaphruti MT, Waikagul J, Maipanich W, Nuamtanong S, Pubampen S. Soil-transmitted helminthiases and health behaviors among schoolchildren and community members in a west-central border area of Thailand. *Southeast Asian J Trop Med Pulbic Health* 2004; 35: 260-66.
3. Ashley EA, Krudsood S, Phaiphun L, Srivilairit S, McGready R, Leowattana W, Hutagalung R, Wilairatana P, Brockman A, Looareesuwan S, Nosten F, White NJ. Randomized, controlled dose-optimization studies of dihydroartemisinin-piperaquine for the treatment of uncomplicated multidrug-resistant falciparum malaria in Thailand. *J Infect Dis* 2004;190(10):1773-82.
4. Bejrachandra S, Kitayaporn D, Kaewkungwal J, Piya-Anant M, Permpikul P, Sirikong M, Siriboonrit U, Chandanayingyong D. HLA class II (DRB1, DQA1 and DQB1) allele and haplotype frequencies among HIV-infection discordant Thai couples. *Asian Pac J Allergy Immunol* 2004;22(2-3):143-51.
5. Brockman A, Singlam S, Phaiphun L, Looareesuwan S, White NJ, Nosten F. Field evaluation of a novel colorimetric method–Double-site Enzyme Linked pLDH Immunodetection (DELI) assay to determine drug susceptibilities of *Plasmodium falciparum* isolates from northwestern Thailand. *Antimicrob Agents Chemother* 2004;48(8):3214.
6. Brockman A, Singlam S, Phiaphun L, Looareesuwan S, White NJ, Nosten F. Field evaluation of a novel colorimetric method—double-site enzyme-linked lactate dehydrogenase immunodetection assay—to determine drug susceptibilities of *Plasmodium falciparum* clinical isolates from northwestern Thailand. *Antimicrob Agents Chemother* 2004;48(4):1426-9.
7. Brouwer AE, Rajanuwong A, Chierakul W, Griffin GE, Larsen RA, White NJ, Harrison TS. Combination antifungal therapies for HIV-associated cryptococcal meningitis: a randomised trial. *Lancet* 2004;363 (9423):1764-7.
8. Buchachart K, Krudsood S, Nacher M, Chindanond D, Rungmatcha P, Kano S, Looareesuwan S. Evaluation of the KAT-Quick Malaria Rapid Test for rapid diagnosis of falciparum malaria in Thailand. *Southeast Asian J Trop Med Public Health* 2004;35(1):35-7.
9. Buchacz K, Hu DJ, Vanichseni S, Mock PA, Chaowanachan T, Srisuwanvilai LO, Gvetadze R, Van Griensven F, Tappero JW, Kitayaporn D, Kaewkungwal J, Choopanya K, Mastro TD. Early Markers of HIV-1 Disease Progression in a Prospective Cohort of Seroconverters in Bangkok, Thailand: Implications for Vaccine Trials. *J Acquir Immune Defic Syndr* 2004;36(3): 853-60.
10. Burivong P, Pattanakitsakul SN, Thongrungkiat S, Malasit P, Flegel TW. Markedly reduced severity of dengue virus infection in mosquito cell cultures persistently infected with *Aedes albopictus* densovirus (AalDNV). *Virology* 2004;329(2):261-9.
11. Butraporn P, Pach A, Pack RP, Masngarmmeung R, Maton T, Sri-aroon P, Nyamete A, Chaicumpa W. The health belief model and factors relating to potential use of a vaccine for shigellosis in Kaeng Koi District, Saraburi province, Thailand. *J Health Popul Nutr* 2004;22(2):170-81.
12. Chaiyaroj SC, Rutta AS, Muenthaisong K, Watkins P, Na Ubol M, Looareesuwan S. Reduced levels of transforming growth factor-beta1, interleukin-12 and increased migration inhibitory factor are associated with severe malaria. *Acta Trop* 2004;89(3):319-27.
13. Cheeramakara C, Nontprasert A, Siripanth C, Tanomsak W, Chularerk U, Sucharit P, Areekul S. Hematological status, plasma vitamin B12 and folic acid levels, and intestinal pathology in rats infected with *Giardia lamblia*. *Southeast Asian J Trop Med Public Health* 2004;35(4): 811-6.
14. Chierakul W, de Fost M, Suputtamongkol Y, Limpaiboon R, Dondorp A, White NJ, van der Poll T. Differential expression of interferon- γ and interferon- γ –inducing cytokines in Thai patients with scrub typhus or leptospirosis. *Clin Immunol* 2004;113(2):140-4.
15. Chierakul W, Rajanuwong A, Wuthiekanun V, Teerawattanasook N, Gasiprong M, Simpson A, Chaowagul W, White NJ. The changing pattern of bloodstream infections associated with the rise in HIV prevalence in northeastern Thailand. *Trans R Soc Trop Med Hyg* 2004;98(11):678-86.
16. Chotivanich K, Sritabal J, Udomsangpetch R, Newton P, Stepniewska KA, Ruangveerayuth R, Looareesuwan S, Roberts DJ, White NJ. Platelet-induced autoagglutination of *Plasmodium falciparum*-infected red blood cells and disease severity in Thailand. *J Infect Dis* 2004;189(6):1052-5.

17. Chotivanich K, Udomsangpetch R, Chierakul W, Newton PN, Ruangveerayuth R, Pukrittayakamee S, Looareesuwan S, White NJ. *In vitro* efficacy of antimalarial drugs against *Plasmodium vivax* on the western border of Thailand. *Am J Trop Med Hyg* 2004;70(4):395-7.
18. Cooper SM, Dhitavat J, Millard P, Burge S. Extensive Grover's-like eruption with lentiginous 'freckling': report of two cases. *Br J Dermatol* 2004;150(2):350-2.
19. Dhitavat J, Fairclough RJ, Hovnanian A, Burge SM. Calcium pumps and keratinocytes: lessons from Darier's disease and Hailey-Hailey disease. *Br J Dermatol* 2004;150(5):821-8.
20. Dondorp AM, Newton PN, Mayxay M, Van Damme W, Smithuis FM, Yeung S, Petit A, Lynam AJ, Johnson A, Hien TT, McGready R, Farrar JJ, Looareesuwan S, Day NP, Green MD, White NJ. Fake antimalarials in Southeast Asia are a major impediment to malaria control: multinational cross-sectional survey on the prevalence of fake antimalarials. *Trop Med Int Health* 2004;9(12):1241-6.
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# TROPMED Presentations 2004

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# RESEARCH ABSTRACTS

FACULTY OF TROPICAL MEDICINE, MAHIDOL UNIVERSITY

# CARE AND TREATMENT OF HIV-INFECTED INJECTING DRUG USERS DURING AN HIV VACCINE EFFICACY TRIAL, BANGKOK, THAILAND

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**BACKGROUND:** Beginning in March 1999, 2,546 injection drug users (IDUs) enrolled in the AIDSVAX B/E Phase III HIV vaccine trial. During the trial, 229 participants became HIV–infected based on serologic testing; 18 of these were HIV–infected at enrollment by nucleic acid testing. The Bangkok Metropolitan Administration (BMA) established HIV treatment guidelines and provided medical care.

**Methods:** HIV–infected participants were followed every 4 months with CD4 and viral load testing. For tuberculosis (TB), isoniazid preventative therapy (IPT) was provided, or if necessary four drug treatment using directly observed therapy (DOTS); those with CD4 <200 were offered cotrimoxazole. Initial BMA antiretroviral (ART) guidelines recommended 2 nucleoside reverse transcriptase inhibitors (NRTI) for those with CD4 <500. In October 2001, this recommendation changed to 2 NRTIs + 1 non-NRTI (HAART) for volunteers taking 2 NRTIs and for volunteers not taking ART with CD4 <200.

**Results:** Of 229 HIV–infected participants, 206 completed TB evaluation. All 15 with active TB received DOTS; 180 (94%) received IPT and 11 refused therapy or had a history of TB treatment. Among the 39 participants with CD4 <200, 30 (77%) received cotrimoxazole; 9 refused, stopped because of side effects, or were lost to follow–up. Under initial guidelines, 79 participants qualified for ART; 34 (43%) started and remained on ART, 23 (29%) decided to stop and have a CD4 >200, 11 (14%) refused therapy or were lost to follow-up, 7 died, and 4 stopped because of side effects. After the October 2001 guideline change, 18 ART naive volunteers developed CD4 <200; 10 (55%) were on HAART at trial completion, 4 were lost to follow-up, 3 stopped because of side effects, and 1 died.

**Conclusion:** HIV-infected participants received care and treatment consistent with BMA guidelines during this HIV vaccine trial, and care, including HAART continues to be provided.

**Presented at:**
The XV International AIDS Conference, 2004 (Poster Exhibition)
Abstract no. MoPeB3350

# CHALLENGES AND APPROACH TO CONDUCTING HIV VACCINE TRIAL IN THE COMMUNITY

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**ISSUES:** Good Clinical Practice, highest standard of treatment and care and ethics in conducting clinical trials, are major concerns especially when a trial is conducted in developing countries. To meet these requirements, there are many challenges in various stages as the trial goes along which include development of clinical sites, standard operating procedures, an process for informed consent, and continuing education of personnel. The subsequent concern is how to maintain the quality of work and morale of staff throughout a multi-year trial.

**Description:** The phase III trial with ALVAC-HIV priming & AIDSVAX® B/E boosting was launched in September 2003 under the leadership of the Ministry of Public Health. The trial will enroll 16,000 HIV-negative volunteers in the communities of the Eastern Seaboard of Thailand. Given the magnitude of the trial, 400 staff were trained to conduct the trial, focused on various activities and divided into recruitment

team, screening team, vaccination team (includes clinical research coordinators, research assistants, counselors and doctors), follow-up team and supervision team. Extensive training and supervision were done to insure the standard of the trial. The informed consent process includes watching video, booklet education, group and individual discussion.

**Lessons learned:** Capacity building, both physical and human, is required and needs strong commitment, knowledge, positive attitudes and innovation from both staff and communities. To provide the highest standard of care attainable by host country requires strong commitment from policy makers. The informed consent process, built on experience from multiple earlier trials, functions very well in these young Thai adults.

**Recommendations:** Community engagement, recruitment and enrollment must continue, while concurrent efforts focus on continued education of staff, maintenance of morale and retention of volunteers.

**Presented at:**
AIDS VACCINE 2004, August 30th-September 1st , 2004 Lausanne, Switzerland

# EFFICACY OF AIDSVAX B/E VACCINES IN INJECTING DRUG USE

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**BACKGROUND:** As a result of HIV/AIDS epidemic in Thailand, a National Plan for HIV/AIDS Vaccine Development and Evaluation was written in 1993. Since then several vaccine studies have been conducted including the phase 3 trial of the AIDSVAX B/E vaccine that began in 1999.

**Methods:** Following informed consent, 2546 HIV-seronegative injection drug users (IDU) meeting the eligibility criteria were randomized to receive AIDSVAX B/E (300 µg of each antigen) or placebo (1:1 ratio) at months 0, 1, and 6, with booster doses at months 12, 18, 24, and 30. All participants were followed for 3 years. The primary end-point was HIV infection. Efficacy and safety analyses were conducted by an independent data analysis group and data safety monitoring board.

**Results:** The follow-up rate for the 2546 IDU enrolled was excellent. There were no significant differences in baseline characteristics or risk behaviors between vaccine and placebo participants. The drop-out rate was 10% for both vaccine and placebo. In the ITT analysis, 106 of 1267 (8.4%) vaccine and 105 of 1260 (8.3%) placebo participants became infected with HIV-1 during the trial. The annualized HIV incidence rate was 3.4 per 100 person-years, 95%CI: 2.8 to 4.1, for both arms. Vaccine efficacy for all strains, subtype E and subtype B was 0.001 (0.308 to 0.238), -0.014 (-0.377 to 0.254) and 0.175 (-0.637 to 0.584), respectively. There were no statistically significant differences in age, gender, or baseline risk behavior between the two groups. Vaccine efficacy on infection and composite endpoint for ITT cohort was 1.1% and 0.6%, respectively.

**Conclusions:** IDU were successfully enrolled in the phase 3 HIV vaccine trial. The study was well conducted, and risk reduction was achieved during the trial. AIDSVAX B/E provides no protection against HIV infection

**Presented at:**
11th Conference on Retroviruses and Opportunistic Infection. February 8-11, 2004. Moscone West, San Francisco, CA

# GEOGRAPHIC DIVERSITY OF HUMAN LEUKOCYTE ANTIGEN (HLA) GENOTYPES AMONG HIV-INFECTED SUBJECTS IN AN INTERNATIONAL HIV VACCINE PREPAREDNESS STUDY

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**BACKGROUND:** HLA Class I genes (A, B, and C) are highly polymorphic, encode for molecules binding viral antigen epitopes, and are critical for induction of cytotoxic T-cell lymphocyte (CTL) response. Development of an epitope-based HIV vaccine that induces CTL response implies the need to address HLA polymorphism in patient populations. Within a study to evaluate cross-clade reactivity to candidate clade B HIV-1 antigens, we characterized HLA alleles in research subjects from five geographically diverse regions. We evaluated differences in distribution of several alleles previously associated with differential rates of progression of HIV infection, and correlated viral load with subject HLA genes of interest.

**Methods:** Subjects were ELISA (or rapid-antigen test confirmed) HIV-positive persons aged 18 to 55 years of age, enrolled in clinics in Brazil (n=55), Cameroon (n=48), Malawi (n=45), South Africa (n=39), and Thailand (n=49). Subjects were excluded if HIV-1 infection had been documented more than 5 years prior to study screening. Sequence specific oligonucleotide assays were used to characterize HLA-A, B, and C alleles. Fisher's exact tests compared the proportion of subjects by site that expressed any of 11 HLA class I alleles reported to be associated with rate of HIV progression (a24, a30, a31, a32, b8, b27, b35, b39, b57, cw4, cw12).

**Results:** HLA data were available for 236 subjects. Among the alleles of interest, a30 and cw4 were the most common, expressed in 23% and 28% of all subjects respectively. A31, a32, b27, b39 and cw12 were the least common, each expressed in fewer than 5% of the subjects. The proportion of subjects expressing a24, a30, b8, b27, b57 each varied by site ($p<0.05$), but did not differ among the remaining alleles. We identified no difference in viral load according to the presence of any of the alleles.

**Conclusions:** Low resolution HLA class I type revealed geographic diversity of several HLA-A and B genes of interest. No differences in viral load according to HLA class I allele was seen in this cross-sectional study.

**Presented at:**
The XV International AIDS Conference, 2004 (Poster Exhibition)
Abstract no. MoPeC3429

# INTERNATIONAL EPIDEMIOLOGY OF HUMAN PRE-EXISTING ANTI-ADENOVIRUS TYPE-5 (AD5) NEUTRALIZING ANTIBODIES IN AREAS REPRESENTATIVE OF POTENTIAL HIV VACCINE TRIAL SITES

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Merck & Co., Inc.

**BACKGROUND:** Replication-defective adenovirus type-5 (Ad5) viruses are presently being studied as candidate vaccine vectors. Pre-existing anti-Ad5 neutralizing antibodies (NA) may impair the ability of these vectors to elicit desired immune responses after vaccination. This study describes the prevalence and epidemiology of anti-Ad5 NA in representative international sites where HIV vaccines may be evaluated.

**Methods:** Subjects at average and high risk for HIV infection, as well as HIV-seropositive subjects, were enrolled into an ongoing study to evaluate the seroprevalence of anti-Ad5 NA to potential live virus vectors in Botswana Brazil (2 sites), Cameroon,

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Malawi, S. Africa and Thailand. Demographic and HIV risk behavior information was obtained by interview. Serum was obtained, frozen and shipped to the US for assay. A validated quantitative assay was used to measure anti-Ad5 NA serum titers. Neutralization titer was defined as the highest dilution of test serum mediating a 50% reduction of virus replication in culture; a titer of <1:18 is considered negative. Titers from international sites were compared to data from ongoing US clinical trials.

**Results:** 1006 subjects (mean age 30.2 yrs) in seven international sites have been evaluated for Ad5 NA (Table). Prevalence of Ad5 NA was higher internationally (91.6%) than in U.S. subjects (61.2 %), ($p < 0.0001$). Thai subjects had higher titers than other international sites ($p < 0.0001$).

Percent Prevalence of Anti-Ad5 Neutralizing Antibody Titer by Country

| Neutralizing Titer | Brazil (n=183) | Botswana (n=68) | Cameroon (n=225) | Malawi (n=49) | S. Africa (n=182) | Thailand (n=299) | Total International (n=1006) | US Subjects (n=779) |
|---|---|---|---|---|---|---|---|---|
| < 18 (negative) | 8.2 | 8.8 | 8.9 | 12.2 | 10.4 | 6.0 | 8.4 | 38.8 |
| 18-200 | 29.5 | 26.5 | 28.9 | 32.7 | 21.4 | 13.7 | 23.2 | 25.4 |
| 201-1000 | 41.0 | 51.5 | 46.2 | 40.8 | 45.1 | 41.8 | 43.8 | 23.6 |
| > 1000 | 21.3 | 13.2 | 16.0 | 14.3 | 23.1 | 38.5 | 24.7 | 12.2 |

**Presented at:**
The XV International AIDS Conference, 2004 (Poster Exhibition)
Abstract no. ThPeC7432

**Conclusions:** Overall anti-Ad5 NA titers varied by geographic location. As HIV vaccine candidates are evaluated in diverse international populations, the geographic variation in pre-existing immunity to candidate vaccine vectors may be of importance in the design of future vaccine trials.

# LACK OF INCREASED HIV RISK BEHAVIOR AMONG INJECTION DRUG USERS PARTICIPATING IN THE AIDSVAX B/E HIV VACCINE TRIAL IN BANGKOK, THAILAND

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**OBJECTIVE:** To determine whether HIV vaccine trial participation leads to increased risk behavior through beliefs about vaccine protection against infection.

METHODS: Changes in risk behavior were evaluated among 2545 injection drug users participating in the AIDSVAX B/E vaccine trial in Bangkok, enrolled from March 1999 to August 2000. Demographic characteristics, beliefs and risk behavior were assessed at baseline and every 6 months thereafter. Risk-reduction counseling was provided at every study visit. Generalized estimation-equation logistic regression analysis was used to study trends in risk behavior and associated factors.

RESULTS: Participants were 93.4% male, their median age was 26 years, and 67.2% had at least secondary education. At baseline, 61.3% were receiving methadone detoxification and 20.9% were receiving methadone maintenance. From baseline to the 12-month follow-up visit, injection drug use decreased from 93.8% to 66.5% ($P < 0.001$) and needle sharing from 33.0% to 17.5% ($P < 0.001$). Multivariate analyses showed earlier follow-up time (at baseline and 6 months) and believing the vaccine to be efficacious associated with more-frequent injecting; younger age and lower education associated with less-frequent injecting. Earlier follow-up time (at baseline), younger age, and injection of methamphetamine and midazolam were associated with more-frequent needle sharing; methadone treatment and injecting less than weekly were associated with less-frequent needle sharing.

CONCLUSIONS: Injection drug use and needle sharing decreased during the first 12 months of the trial. No increases in risk behavior in relation to beliefs about vaccine protection against HIV infection could be identified.

**Published in:** *AIDS* 2004;18:295-301.

# PHASE I/II STUDY OF A CANDIDATE VACCINE DESIGNED AGAINST THE B AND E SUBTYPES OF HIV-1

**Pitisuttithum P[1], Berman PW[2], Phonrat B[1], Suntharasamai P[1], Raktham S[3], Srisuwanvilai LO[3], Hirunras K[3], Kitayaporn D[1], Kaewkangwal J[1], Migasena S[2], Sheppard HW[4], Li E[2], Chernow M[5], Peterson ML[2], Shibata R[6], Heyward WL[2], Francis DP[2]**

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**Published in:** *J Acquir Immune Defic Syndr* 2004;37:1160-5.

A phase I/II trial of a candidate vaccine to prevent HIV infection was carried out in Bangkok, Thailand, testing AIDSVAX B/E (VaxGen, Inc., Brisbane, CA), a bivalent subunit vaccine prepared by combining recombinant gp120 from a subtype B virus (HIV-$1_{MN}$) with gp120 from a subtype E virus (HIV-$1_{A244}$) in alum adjuvant. The studies provide human data on the immunogenicity of various dose combination of non-subtype B vaccine antigens. The results suggest that AIDSVAX B/E is safe and immunogenic in humans. The optimal dose for humans in developing countries was 300 µg of each antigen (B and E). Clade E responses were measurably increased by immunizing with gp120 B/E over B alone. Using the B/E combination did not interfere with the response to either clade. Antibodies to AIDSVAX B/E were able to bind to oligomeric gp120 on the surface of cells infected with primary isolates of HIV-1.

# PRELIMINARY RESULTS OF A PHASE III HIV VACCINE EFFICACY TRIAL AMONG INJECTING DRUG USERS IN THAILAND

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**BACKGROUND:** The world's first phase III HIV vaccine trial in Asia was successfully completed in June 2003 in Thailand.

**Methods:** The HIV vaccine trial started in March 1999. The trial was a collaborative effort involving the Bangkok Metropolitan Administration, the Thailand Ministry of Public Health (MOPH), Mahidol University, the U.S. Centers for Disease Control and Prevention (CDC), the Thai MOPH – U.S. CDC Collaboration, and VaxGen Inc. HIV-seronegative IDUs were randomized (1:1) to receive 7 doses of AIDSVAX B/E or placebo in a blinded fashion over 30 months. AIDSVAX B/E is a bivalent rgp120 vaccine developed to protect against HIV-1 subtypes B and E. Participants were followed for 36 months.

**Results:** From March 1999 through August 2000, 4,943 IDUs were screened for enrollment; 1,689 were HIV-seropositive, 708 were excluded for other reasons, and 2,546 were enrolled. Immunization compliance was high (>97%) and volunteer follow-up was excellent (>95%). No vaccine-related serious adverse events were reported. Among enrolled participants, 229 became HIV-infected based on serologic testing; 18 of these were HIV-infected at enrollment by nucleic acid testing. Among the 211 who became HIV-infected during trial follow-up, 105 received placebo and 106 vaccine. HIV-1 subtype E was identified in 164 (77.7%) infected participants and subtype B in 47 (22.3%). The point estimate of vaccine efficacy was 0.1% (95% confidence interval, -30.8%, 23.8%). The HIV incidence rate was 3.1% per year. Reported frequency of drug injection and needle sharing declined significantly during the trial.

**Conclusion:** AIDSVAX B/E does not protect IDUs from HIV infection. The annualized HIV incidence was 3.1%. Drug injection and needle sharing declined, suggesting effective risk reduction counseling. With appropriate infrastructure, preparation, and training, scientifically sound and ethical phase III HIV vaccine trials can be completed among IDUs.

**Presented at:**
The XV International AIDS Conference, 2004 (Oral Abstract session) Abstract no. ThOrA1427

# RECRUITMENT, SCREENING AND CHARACTERISTICS OF INJECTION DRUG USERS PARTICIPATING IN THE AIDSVAX B/E HIV VACCINE TRIAL, BANGKOK, THAILAND

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**OBJECTIVES:** To describe recruitment, screening and baseline characteristics of injection drug users (IDU) participating in a phase III HIV vaccine (AIDSVAX B/E; VaxGen, USA) trial and to compare enrollment characteristics between trial participants and 1209 IDU from a 1995-1998 vaccine trial preparatory cohort for changes that might impact trial design assumptions. METHODS: Enrollment for both studies was conducted at Bangkok narcotic treatment clinics, where a standardized questionnaire was administered on demographics, risk behavior and incarceration history over the previous 6 months.

RESULTS: During 1999-2000, 4943 IDU were screened for enrollment; successful sources of recruitment included clinic attendees (43.4%), an IDU referral program (20.4%) and preparatory cohort participants (14.7%). Of those screened, 1689 (34%) were HIV seropositive (HIV subtype B 23.6%; subtype E 76.4%). Of the 2545 enrolled, 93.4% were male. Compared with cohort IDU, trial IDU were younger (mean age: 28.8 versus 31.3 years), better educated (secondary level or higher: 67.2% versus 58.7%), and less likely to inject drugs daily (39.4% versus 90.4%); they were more likely to have been incarcerated (78.4% versus 65.7%), have recently injected stimulants (14.8% versus 5.8%) and tranquilizers (11.5% versus 2.3%), and obtained needles/syringes from a source other than a pharmacist (7.2% versus 3.9%) (all P < or = 0.003).

CONCLUSIONS: IDU at high risk for HIV have been successfully enrolled in the AIDSVAX B/E efficacy trial. Only minor epidemiologic differences were found at enrollment between trial and preparatory cohort IDU. The latter has proven critical in guiding trial design; results are expected in late 2003.

**Published in:** *AIDS* 2004;18:311-6.

# RETENTION OF SUBJECTS IN A MULTI-SITE INTERNATIONAL EPIDEMIOLOGY STUDY IN PREPARATION OF LARGE SCALE HIV VACCINE EFFICACY TRIALS

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**BACKGROUND:** Testing potential HIV vaccine candidates in efficacy trials is a complex task. Appropriate populations must be identified and the feasibility of conducting studies at the site of interest must be assessed. This study evaluated the feasibility of subject enrollment and retention and efficiency of cell isolation procedures for study sites participating in a multisite HIV epidemiology study designed to examine in vitro cross-clade immune responses to candidate HIV-1 antigens.

Methods: Study approvals were obtained from local IRBs and appropriate government bodies. Written informed consent and baseline demographic information was obtained from all subjects. Whole blood was collected at 8 to 10 week intervals for a minimum of 3 visits. Peripheral blood mononuclear cells (PBMCs) were isolated, frozen, and shipped to the US to estimate in vitro immune responses to HIV-1 antigens using ELISPOT IFN-assays. An acceptable cell yield was defined as $1x10^7$ PBMCs per 10mL of blood isolated.

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**Results:**

| | Brazil | Thailand | South Africa | Malawi | Cameroon | Botswana* |
|---|---|---|---|---|---|---|
| Subjects recruited | 60 | 77 | 50 | 66 | 52 | 57 |
| Subjects eligible | 56 | 50 | 43 | 49 | 46 | 50 |
| Subjects retained for at least 3 visits | 54 (96%) | 46(92%) | 37(86%) | 44(90%) | 46(100%) | 46(92%) |
| Percent of acceptable cell yields | —** | 98% | 96% | 95% | 96% | 73% |

* Subject follow-up is on-going; 3 visits still pending. Cell yield only includes partial data.
** Data not shown because the cell isolation procedures differed from the other participating

**Conclusions:** Subjects were successfully consented, enrolled, and retained in the study. Across study sites, subject retention for at least three visits was above 90%. Despite logistical challenges at sites and transport times of 2 to 3 days, cell viability was high and shipments were received on a timely basis. Future HIV vaccine efficacy trials are feasible provided that the logistical issues are resolved and appropriate subject populations can be recruited and retained over multiple visits.

**Presented at:**
The XV International AIDS Conference, 2004 (Poster Exhibition) Abstract no. ThPeC7454

# RISK FACTORS AND INCIDENCE OF HIV INFECTION AMONG INJECTING DRUG USERS (IDUS) PARTICIPATING IN THE AIDSVAX® B/E HIV VACCINE EFFICACY TRIAL, BANGKOK

**S Vanichseni[1], F van Griensven[2], B Metch[3], P Pitisuttithum[4], M Martin[2], D Kityaporn[4], JW Tappero[2], A Luck[5], K Choopanya[1]**

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Bangkok Vaccine Evaluation Group

**BACKGROUND:** IDUs in Bangkok were recruited in the AIDSVAX B/E vaccine efficacy trial. We determined risk factors for incident HIV infection.

**Methods:** The AIDSVAX B/E trial was conducted from March 1999 to June 2003. HIV-seronegative IDUs received either AIDSVAX B/E or placebo. Risk reduction counseling, a risk behavior interview and HIV testing were done at 6-month intervals. Baseline demographic and risk behavior data were used to predict incident HIV infection in Cox proportional hazard analyses.

**Results:** 2,546 IDUs were enrolled; their median age was 26 years, 93.4% were male and 95.0% had at least primary education. Eighteen IDUs were HIV-infected at baseline and 211 became HIV-infected during the study (cumulative incidence: 8.3%, 95% CI 7.3% - 9.4%). During the trial, significant decreases in injecting (from 93.8% to 50.5%) and in needle sharing (33.0% to 16.2%) were observed. In univariate analysis, injecting, injecting heroin, higher frequency of injecting, re-use of needles, serving time in prison, receiving methadone detoxification and injecting while incarcerated (in jail or prison) were associated with increased risk for incident HIV infection (all $p<0.05$); receiving methadone maintenance ($p<0.003$) and having a casual sex partner were associated with decreased risk ($p<0.04$). In multivariate analysis, higher frequency of injection (adjusted hazard ratio [(AHR)] = 1.6, $p<0.05$), receiving methadone detoxification (AHR = 1.7, $p<0.002$) and injecting while incarcerated (AHR = 2.6, $p<0.002$) remained independently associated with increased risk for incident HIV infection; having a casual sex partner (AHR = 0.6, $p<0.04$) remained associated with decreased risk.

**Conclusions:** Despite reductions in HIV risk behavior, participants in the trial remained at increased risk for HIV infection through injection drug use, particularly during incarceration. Effective interventions are needed to address this ongoing epidemic of HIV infection in Bangkok IDUs.

**Presented at:**
The XV International AIDS Conference, 2004 (Poster presentation)Abstract no. TuPpC2043

# SAFETY AND IMMUNOGENICITY OF AN HIV SUBTYPE B AND E PRIME-BOOST VACCINE COMBINATION IN HIV-NEGATIVE THAI ADULTS

**Nitayaphan S, Pitisuttithum P, Karnasuta C, Eamsila C, de Souza M, Morgan P, Polonis V, Benenson M, VanCott T, Ratto-Kim S, Kim J, Thapinta D, Garner R, Bussaratid V, Singharaj P, el-Habib R, Gurunathan S, Heyward W, Birx D, McNeil J, Brown AE; Thai AIDS Vaccine Evaluation Group**

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**ALVAC-HIV** (vCP1521) and AIDSVAX B/E were evaluated in a phase 1/2 trial of human immunodeficiency virus (HIV)-negative Thai adults. Of 133 volunteers enrolled, 122 completed the trial. There were no serious vaccine-related adverse events, nor were there intercurrent HIV infections. Lymphoproliferative responses to glycoprotein 120 E were induced in 63% of the volunteers, and HIV-specific CD8 cytotoxic T lymphocyte responses were induced in 24%. Antibody responses increased in frequency and magnitude in association with the dose level of AIDSVAX B/E. Binding and neutralizing antibodies to the MN strain were induced in 100% and 98%, respectively, of the volunteers receiving 600 microg of AIDSVAX B/E, and such antibodies to E strains were induced in 96% and 71%, respectively, of these volunteers. This vaccine combination was well tolerated and was immunogenic, meeting milestones for advancement to phase 3 evaluation.

**Presented at:**
J Infect Dis. 2004 Aug 15;190(4):702-6. Epub 2004 Jul 20.

# SOCIAL IMPACT AND HARM AMONG INJECTING DRUG USERS (IDUS) IN A PHASE III HIV VACCINE TRIAL IN THAILAND

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**BACKGROUND:** In June 2003, a phase III HIV vaccine trial was completed among injecting drug users (IDUs) in Bangkok. Trial participants were potentially subject to study-related social harms such as discrimination or stigmatization because of identification with a high risk group or false positive HIV test results due to vaccine-induced antibody.

**Methods:** 2,546 IDUs were enrolled in the 36 month vaccine trial. Volunteers received education, counseling, and monitoring targeted to reduce HIV risk behaviors and identify study related social harms at 6-month (HIV-uninfected) or 4-month (HIV-infected) visits. If a social harm was reported, a questionnaire was administered to characterize the reported social harm, describe its impact, and track the event until it was resolved.

**Results:** During the vaccine trial, 39 social harm events were reported by 37 participants; 33 (85%) events were disturbances in personal relationships, 3 (8%) involved loss of employment, 2 (5%) were medically related, and 1 (3%) was a housing problem. Participants reported disturbances in personal relationships because family or friends suspected vaccine would cause HIV infection (n=14) or injury (n=5). The quality of life impact of these events was characterized by trial volunteers as minimal by 31, moderate by 7, and major by 1 volunteer. All but 2 events were resolved by the end of the trial and there were no reports of social harm events due to vaccine – inducedpositive HIV test results.

**Conclusions:** Less than 2% of participants reported study-related social harms. This low rate may be due to effective counseling and education provided during the trial, or perhaps because of cultural differences in the definition and experience of social harms among these Thai IDUs. Most reported social harms were due to disturbances in personal relationships. Interventions, including outreach to family and friends, should be made available during HIV vaccine trials to address social harms as they occur.

**Presented at:**
The XV International AIDS Conference, 2004 (CD Only) Abstract no. C11162

# ACETYLCHOLINESTERASE AND CHOLINESTERASE ACTIVITIES IN *GIARDIA LAMBLIA* TROPHOZOITES CULTURED *IN VITRO*

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*Keywords: acetylcholinesterase, cholinesterase,* Giardia lamblia *trophozoites,* in vitro

**AXENIC** culture of *Giardia lamblia* trophozites *in vitro* was conducted from patients infected with *Giardia lamblia*. The cholinesterase (ChE) and acetylcholinesterase (AChE) activities were determined in cultured Giardia trophozoites. The enzyme activities were found in boh tissue-bound and tissue-free forms. There was low ChE and AChE enzyme activities in trophozoites (1.6095 ± 1.0981; 0.9626 ± 0.1322; 0.1387 ± 0.0783; 0.0752 ± 0.0877 Units/mg protein, respectively). The tissue-bound and tissue-free ChE enzymes were found in a greater amount than tissue-bound and tissue-free AChE enzymes. The presence of these enzymes in Giardia may involved in the motility of Giardia trophozoites.

**Presented at:**
Joint international Tropical Medicine Meeting 2004, Bangkok, Thailand. 29 November - 1 December 2004.

# CHOLINESTERASE AND ACETYLCHOLINESTERASE ACTIVITIES IN *GIARDIA LAMBLIA* TROPHOZOITES CULTURED *IN VITRO*

**Cheeraratana Cheeramakara[1], Apichart Nontprasert [2], Chutatip Siripanth[3], Pramuanmarn Sucharit[3], Kriyaporn Songmuaeng[1], Nophachai Suthisai[1], Suvit Areekul[1]**

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*Keywords: cholinesterase, acetylcholinesterase,* Giardia lamblia *trophozoites,* in vitro

**AXENIC** culture of *Giardia lamblia* trophozoites *in vitro* was conducted from patients Giardiasis. The cholinesterase (ChE) and acetylcholinesterase (AChE) activities were determined in cultured Giardia trophozoites. The enzyme activities were found in boh tissue-bound and tissue-free forms with low ChE and AChE enzyme activities (1.6095 ± 1.0981; 0.9626 ± 0.1322; 0.1387 ± 0.0783; 0.0752 ± 0.0877 Units/mg protein), respectively. The tissue-bound and tissue-free ChE enzymes were found in a greater amount than tissue-bound and tissue-free AChE enzymes. The presence of these enzymes in *G. lamblia* may be involved in the motility of Giardia trophozoites.

**Published in:**
Southeast Asian J Trop Med Public Health

# CALCIUM PUMPS AND KERATINOCYTES: LESSONS FROM DARIER'S DISEASE AND HAILEY-HAILEY DISEASE

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**Published in:**
Br J Dermatol 2004;150(5): 821-8.
Review.

◎ **DARIER'S** disease and Hailey-Hailey disease are autosomal dominantly inherited skin disorders in which desmosomal adhesion between keratinocytes is abnormal. *ATP2A2* and *ATP2C1* have been identified as the causative genes for Darier's disease and Hailey-Hailey disease, respectively. *ATP2A2* encodes the sarco(endo)plasmic reticulum $Ca^{2+}$-ATPase isoform 2 (SERCA2) pump, while *ATP2C1* encodes a secretory pathway $Ca^{2+}/Mn^{2+}$-ATPase (SPCA1) found in the Golgi apparatus. We review recent work into the function of these pumps in human keratinocytes and discuss how mutations in these genes might cause these diseases by altering the formation or stability of desmosomes.

# 'GROVEROID' DARIER'S DISEASE

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**Published in:**
Br J Dermatol 2004;150(3):600-2.

Abstract not available

# EXTENSIVE GROVER'S-LIKE ERUPTION WITH LENTIGINOUS 'FRECKLING': REPORT OF TWO CASES

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**Published in:**
Br J Dermatol 2004;150(2):350-2.

◎ **WE** have described two females with extensive freckling and scaly lesions and conclude that they have a widespread form of Grover's disease associated with lentiginous sun-induced 'freckling'. We report these cases to draw attention to an unusual pattern of Grover's disease that can simulate Darier's disease.

# MOLECULAR DIAGNOSIS OF SCRUB TYPHUS IN PATIENTS PRESENTING WITH ACUTE FEBRILE ILLNESS

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**SCRUB** Typhus is a major cause of acute febrile illness in the Asia-Pacific region. The disease is caused by *Orientia tsutsugamushi*, an obligate intracellular Gram negative coccobacillus transmitted by trombiculid mites. In Thailand, more than 200,000 cases of acute febrile illness were reported in 1999. A prospective study performed by the Wellcome Unit of acute febrile illness in patients presenting to a general hospital in Udon Thani, northeasthern Thailand between October 2000 and December 2002 found that 25% of 1,263 cases had scrub typhus based on immunofluorescent antibody (IFA) testing. Presenting features of scrub typhus are often indistinguishable from those of other acute febrile illnesses such as leptospirosis, murine typhus and dengue fever. Rapid diagnosis would be clinically useful in patient management. Molecular diagnosis based on the polymerase chain reaction (PCR) has been developed. Using the16S ribosomal RNA gene, primers were designed using sequence for *Orientia tsutsugamushi* to give a product size of 220 bp. The PCR primers were designed to be specific for this species, and did not give an amplification product when used with genomic DNA from *R. prowazekii*, *R. conorii*, *R. honeii*, *R. australis*, *R.typhi* and *Leptospira spp*. DNA was extracted from whole blood taken on admission from 511 patients presenting with acute febrile illness. The use of PCR as diagnostic tool for scrub typhus have been evaluated against the current gold standard IFA. The sensitivity and specificity of PCR versus gold standard serology for the diagnosis of scrub typhus were 52.6% and 99.7 % respectively.

**Presented as:**
an oral Presentation, Joint International Tropical Medicine Meeting 2004, 29 November –1 December 2004, Ambassador Hotel, Bangkok, Thailand.

# TREATMENT TRIALS OF ACUTE AND MAINTENANCE ANTIBIOTIC THERAPY FOR PATIENTS WITH MELIOIDOSIS

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**TWO** antibiotic regimens are commonly used in Thailand for the initial treatment of severe melioidosis. These are ceftazidime in combination with trimethoprim-sulphamethoxazole (TMP-SMX), and ceftazidime monotherapy. It is not know whether use of the combination regimen provides additional benefit.

We have conducted an open-label randomized trial of these two regimens in patients with acute severe melioidosis in two large hospitals in Ubon Ratchathani and Khon Kaen, NE Thailand. The primary end point was in-hospital mortality. Of the 235 patients with culture-confirmed melioidosis, 48 (20%) died. Of these, 28 (12%) died 48 hours or more after the time of admission. There was no difference in death between the two treatment groups for either all deaths (p = 0.64, OR 0.69 95% CI 0.29-1.6), or death occurring after 48 hours (p = 0.66 OR 0.54, 95% CI 0.17-1.7) On Cox analysis, underlying renal disease and positive blood culture on admission were associated with death. Drug regimen was not associated with death in this model.

We conclude that the addition of TMP-SMX to ceftazidime therapy during the initial treatment of acute melioidosis dose not lead to a reduction in the risk of death.

**Present at:**
Joint International Tropical Medicine Meeting 2004, Bangkok, Thailand 29 November-1 December 2004

# LIVER OF CEREBRAL MALARIA PATIENT WAS VOID OF RETINOL STORE: A FIRST OBSERVATION ON VITAMIN A-STORING CELLS FROM AUTOPSY SPECIMEN

**Wichai Ekataksin[1,2], Narumon Chanwimalueang[1], Gedsuda Pattanapen[1], Borimas Hanboonkunupakarn[1], Thamrong Chirachriyavej[3], Mario Riganti[4], Emsri Pongponratn[4], Srivicha Krudsood[5], Polrat Wilairatana[6], Sornchai Looareesuwan[7]**

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**VITAMIN** a supplement at high doses reportedly can help growth in children with malaria (Shankar, 2000; Serghides and Kain, 2002: Villamor et al, 2002). Whether the results are due to nutritional or therapeutic effect, or both remains unclear. Literature about pathobiology of malarial liver is extremely sparse. Of rare occasion, we exmined the liver of a man aged 22 years, body weight 52 kg, with *Plasmodium falciparum* infection who was referred to our hospital for severe cerebral malaria. The patient died at day 12 after admission, and autopsy conducted under informed consent of relatives. The removed dark brown liver, weighing 1,410 g, was investigated by fluorescence microscopy for vitamin A autofluorescence (Wake et al, 1987) and Golgi-Kopsch chromic silver technique (Wake *et al*, 1988) plus opticoconfocal depth-reconstruction imaging (Ekataksin *et al*. 2003) for visualization of hepatic stellate cells or retinol-storing arachnocytes (Ekataksin and Kaneda, 1999). Control liver was obtained from a forensic autopsy of a 45-year-old male with acute heart failure. Under wide ultraviolet, 330-385 nm excitation, the 50~100-mm-thick frozen sections of normal liver appeared with myriads of brightly glaring fluorescent spots distributed homogeneously in liver lobules, representing the lipid droplets containing vitamin A. The fluorescence faded in 20-200 seconds. Higher magnifications revealed that each spot, located 30-50 mm apart along the sinusoids, was composed of globules of various of various sizes. Fluorescence was present within the lobules only, not found of the stroma. In malarial liver, the lobules were totally nonfluorescent. Hepatocytes were yellowish brown with distinct accentuation of light blue periportally. Dark pigments were discernible in the sinusoids. Under Golgi method, human arachnocytes exhibited a striking irregular shape, measuring 40-60 mm with several elongate slender processes characterized by knobs, segmental isthmi, and flexes, reminiscent of a rhizome studded with thread-like roots. Cell body was recognized with multiple lipid droplets. In malaria, the arachnocytes were visualized with more abundant cytoplasmic processes; lipid droplets were null or almost absent. The cells were not demonstrable in hematoxylin-eosin preparation, where bile plugs, intrahepatocellular biliary lysosomes, and phagosome-laden Kupffer cells were prevailing. Findings are clear that in the malarial patient, liver store of vitamin A is apparently diminished or depleted. Whether/How retinol metabolism is involved in the pathogenesis can not be determined with certainty in this single case observation. The present study is the first of its kind in demonstrating the retinol autofluorescence and in visualizing the arachnocyte reconstruction of human liver.

Supported in port by RBD Project Grant # 4703 (to WE), National Science and Technology Development Agency, and by Toxicology Graduate Program (to NC), Faculty of Science, Mahidol University.
**Present at:**
Joint International Tropical Medicine Meeting 2004, Bangkok, Thailand 29 November-1 December 2004

# ASSESSING THE UTILITY OF MICROSATELLITE MARKERS FOR *PLASMODIUM VIVAX*

**Mallika Imwong[1], Shalini Nair[2], Sasithon Pukrittayakamee[1], Sornchai Looareesuwan[1], Nick Day[3,4], Nicholas J White[3,4], Tim JC Anderson[2]**

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**THE** present study describes practical protocols based on microsatellite loci for genotyping *Plasmodium vivax*. The study purposes were to describe the population structure of *P.vivax* collected from 3 regions of Asia and to assemble a panel of informative markers for assessing multiple clone carriage and discriminating between new, recrudescent and relapse infections. To achieve this we located pure repeats of between 2-10 bp in existing sequence data for *P.vivax*, and designed oligo to amplify 5-di, 5tri-, 5 tetranucleotide repeats and 6 sequences containing repeats between 5 and 8bp in size. A panel of 6 samples from Thailand were tested and 16 useful markers were generated. Of these markers four were free of stutter peaks and highly variable (He = 0.78-0.94) Using microsatellite technique, genotyping were completed applying the 4 generated markers in 300 samples collected from Thailand, Culcutta (India), and Myanmar. Frequencies of multiple infections were high in all areas. Microsatellite markers reveal low but highly significant genetic differentiation between parasite populations in three areas.

**Present at:**
Joint International Tropical Medicine Meeting 2004, Bangkok, Thailand 29 November-1 December 2004

# PHENOTYPIC CHARACTERISTIC OF *P. FALCIPARUM* ASSOCIATED WITH SEVERE MALARIA

**Kesinee Chotivanich[1], Duangdao Nantakomol[1], Rachanee Udomsangpetch[2], Sasithon Phukrttayakamee[1], Arjen Dondorp[3], Sornchai Looareesuwan[1], Nicholas PJ Day[1,3], Nicholas White[1,3]**

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**MANY** factors both host and parasite derived, determine disease severity in falciparum malaria. An important factor associated with adverse outcome is a reduction in the deformability of erythrocytes. Host red cells become rigid after parasite invasion. But also, uninfected red cells reduced deformability in severe malaria, which may result from exposure to products released by the parasites. These rigid red cells contribute to capillary occlusion. Parasite virulence factors include parasite multiplication capacity (Chotivanich et al, 2002). We found that the parasites with a higher multiplication capacity and less selective erythrocte invasion were more likely to produce severe malaria. Cytoadherence or the adhesion of infected red cells to the endothelial cells also contributes to the pathophysiology of severe malaria. *P.falciparum* does cytoadhere, but *P.vivax* which causes more benign disease does not. Recently, we have shown platelet induced autoagglutination of *P.falciparum*-infected red cells to be associated with disease severity. In contrast agglutination of *P.vivax* is rare. All these properties can be viewed as virulence factors.

Finally, we measured cell derived microparticles in blood malaria patients. by using flow cytomertry. We found that the total number of microparticles was higher in malaria patients compared to healthy donors. We showed that to microparticles derive from red cells, endothelial cell and platelets. These particles contain the surface proteins mediating coagulation and adhesion. Their generation and specific pathophysiology roles are further investigated.

**Present at:**
Joint International Tropical Medicine Meeting 2004, Bangkok, Thailand 29 November-1 December 2004

# ANTIMALARIAL TRIAL IN THAILAND

**Sornchai Looareesuwan, Polrat Wilairatana, Srivicha Krudsood, Udomsak Silachmroon**

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◎ **NEW** antimalarial drugs that have been investigated at the Hospital for Tropical Diseases, Faculty of Tropical Medicine, Mahidol University, in recent years are as follows. Atovaquone, a hydroxynaphthoquinone, was evaluated and it was found that atovaquone alone proved safe and effective. All patients treated had clinical cure, however, one third of patients had late recrudescence (RI). When it was combined with proguanil, the cure rate increased to 100%. This combination has now been developed into a fixed drug named Malarone." Artemisinine derivatives such as artesunate, artemether, arteether and dihydroartemisinin are also tested at the Bahgkok Hospital for Tropical Diseases. Artesunate and artemether alone at a total dose of 600 to 750 mg. given over 5-7 days produced cure rates of 80 to 95%. Artesunate or dihydroartemisinin suppositories at a dose of 10 mg/kg/day have been proved successful for the treatment of severe malaria. The artemisinin derivatives, (4 mg/kg/day) when used in combination with mefloquine (8 mg/kg/day) given once a day for 3 days gave improved cure rates, up to 95-100%. Dihydroartemisinin alone with a total dose of 480 mg given oven 5 days gave a cure rate of 90%. Arteether, a WHO/TDR supported drug, has been evaluated in the Hospital and now has been registered for use (the same dose of artemether) in severe malaria under the name Artemotil." Other combinations (artemisinin derivatives combined with tetracycline or doxycycline and mefloquine combined with tetracycline or doxycycline) have also been evaluated with improvement in cure rates. Recently, a fixed drug (artemether plus lumefantrine) named Coartem" (six dose given over 72 hours) proved to be a safe and effective drug (cure rate over 95%) for the treatment of falciparum malaria and it has been registered for use in many western countries. At present, studies with combinations of artemisinin derivatives plus mefloquine (in various doses and durations of treatment) are being investigated. Recently we have finished the double-blind, randomized, comparative study of 200 patients (adults and children) with falciparum malaria treated by a pre-packed blister approach (4 mg/kg/day artesunate and 8 mg/kg/day given once a day for 3 days) and found that this approach proved safe and effective and this approach could translate clinically into a better patient compliance. Other fix-combinations (Artecom", Artekin") proved safe and efficious (cure rate over 98%) and could be an alternative antimalarial drugs. In general, artemisinin derivatives (12 mg/kg total dose given in 3 days) combined with mefloquine (25 mg/kg total dose given in 3 days) have been a standard regimen for the treatment of multidrug resistant falciparum malaria in Thailand. Until proven other wise, drug combinations are still recommended for all adult patients suffering from acute uncomplicated falciparum malaria contracted in multidrug resistant areas.

The treatment for uncomplicated malaria is aimed at producing a radical cure using the combination of either (1) artesunate (4 mg/kg/day) plus mefloquine (8 mg/kg/day) for 3 days; (2) a fixed dose of artemether and lumefantrine (20/120 mg tablet) named Coartem, (4 tablets twice a day for three days for adults weighing more than 35 kg); (3) quinine 10 mg/kg 8-hourly plus tetracycline 250 mg 6-hourly for 7 days (or doxycycline 200 mg once a day for 7 days as an alternative to tetracycline) in patients aged 8 years and over; and (4) a combination of atovaquone and proguanil called Malarone" (in adult, 4 tablets given daily x 3 days). In treating severe malaria, early diagnosis and early treatment with a potent antimalarial drug is recommended to save the patient's life. The antimalarial drugs of choice are: intravenous quinine or a parenteral from of an artemisinin derivative (artesunate i.v./i.m. 2.4 mg/kg followed by 1.2 mg/kg injection at 12 and 24 hr and then daily for 5 day; artemether i.m. 3.2 mg/kg injection followed by 1.6 mg/kg at 12 and 24 hrs and then daily for 5 days; arteether i.m.(Artemotil") with the same dose of artemether; artesunate suppository (5 mg/kg)

given rectally 12 hourly for 3 days). Oral artemisinin derivatives (artesunate, artemether, dihydroartemisinin with the dose 4 mg/kg/day should replace parenteral forms when patients can tolerate oral medication). Oral mefloquine (25 mg/kg divided into two doses 8 hrs apart) should be given at the end of the artemisinin treatment course to reduce recrudescence.

The treatment of vivax malaria in Thailand is still using chloroquine and primaquine. However with the ineffective to primaquine (15 mg/kg/day for 14 days with relapse of 15%) the higher dose (30 mg/kg/day for 14 days) is recommended. The efficacy studies primaquine in various regimen given together with Sulfadoxin/Pyrimethamine or artemisinin derivatives are in progress. Tefenoquine" phase III study in the planning stage for clinical trial in our setting in Thailand is in progress.

**Present at:**
Joint International Tropical Medicine Meeting 2004, Bangkok, Thailand 29 November-1 December 2004

## QUANTITATIVE REAL TIME POLYMERASE CHAIN REACTION FOR DETECTING *ORIENTIA TSUTSUGAMUSHI* IN HUMAN SPECIMENS

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**SCRUB** typhus is a common zoonosis of rural Asia. The causative organism, *Orientia tsutsugmushi*, has been detected by nested PCR in human specimens and by real-time quantitative polymerase chain reaction (qPCR) in animal specimens. Here, we used a 47-kD qPCR assay to detect *O. tsutsugamushi* in specimens from patients with proven scrub typhus. The assay was more sensitive than was mouse inoculation; it was reactive in whole blood specimens from all 10 isolate-positive patients and in 7 of 17 isolate-negative individuals ($p = 0.003$, Fishers two-tailed exact test) As few as 1,076 *O. tsutsugamushi* copies/L were detected in whole blood. The assay was specific; it was unreactive in all 12 individuals without *O. tsutsugamushi* infection. This is the first demonstration of a sensitive and specific real-time qPCR assay for human scrub typhus infection.

**Present at:** Joint International Tropical Medicine Meeting 2004, Bangkok, Thailand 29 November-1 December 2004

## RANDOMIZED TRIAL OF 3-DOSE REGIMENS OF TAFENOQUINE (WR238605) VERSUS LOW-DOSE PRIMAQUINE FOR PREVENTING *PLASMODIUM VIVAX* MALARIA RELAPSE

**Douglas S. Walsh[1], Polrat Wilairatana[2], Douglas B. Tang[3], D. Gray Heppner, Jr.[1], Thomas G. Brewer[1], Srivicha Krudsood[2], Udomsak Silachamroon[2], Weerapong Phumratanaprapin[2], Duangsuda Siriyanonda[1] and Sornchai Looareesuwan[2]**

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**TAFENOQUINE** (TQ) is an 8-aminoquinoline developed as a more effective primaquine (PQ) replacement. In a previous dose ranging study in Thailand, 3 TQ regimens with total doses ranging from 500 mg to 3000 mg prevented *P. vivax* malaria relapse in most patients when administered 2 days after completing a blood schizonticidal dose of chloroquine (CQ). Here, to expand upon those findings, improve convenience, and begin comparing TQ with PQ, 80 patients with *P. vivax* were randomized to 1 of 5 treatments 1 day after completing a blood schizonticidal dose of CQ: (A) TQ 300 mg daily for 7 days (n = 18), (B) TQ 600 mg daily for 3 days (n = 19), (C) TQ 600 mg as a single dose (n = 18), (D) no further treatment (n = 13), or (E) PQ base 15 mg daily for 14 days (n = 12). Per protocol follow-up was a minimum of 8

weeks, with additional follow-up to 24 weeks. Patients completing at least 8 weeks of follow-up (or relapsing) were 46 of 55 for TQ, 10 of 13 for CQ only, and 12 of 12 for CQ + PQ. There was 1 relapse in CQ + TQ (Group C), 8 in CQ only, and 3 in CQ + PQ. Protective efficacy based on reduction in incidence density for all CQ + TQ versus CQ + PQ was 92.6% (95% CI: 7.3% to 99.9%; 2p = 0.042). Tafenoquine doses as low as a single 600 mg dose may be useful in preventing *P. vivax* relapse in Thailand.

**Publish in:**
*Clinical Infectious Diseases* 2004;39: 1095-103.

## POLYMORPHISMS OF *HLA-B* AND *HLA-DRB1* GENES IN THAI MALARIA PATIENTS

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*Key words: malaria, HLA, Thailand*

**THE** high degree of polymorphism of human leukocyte antigen (*HLA*) genes has been suggested to result from natural selection against susceptibility to a variety of infectious pathogens, including malaria. HLA molecules are considered to play a crucial role in the host defense against malarial infection, and different *HLA* class I and class II alleles have been reported to be associated with reduced susceptibility to malaria or severity of malaria in different populations. To test for associations between *HLA* alleles and severity of malaria in a Thai population, polymorphisms of *HLA-B* and *HLA-DRB1* genes were investigated in 472 adult patients in northwest Thailand with *Plasmodium falciparum* malaria. In this study, malaria patients were classified into three groups: mild malaria, non-cerebral severe malaria, and cerebral malaria. Our results revealed that the allele frequencies of *HLA-B46*, *-B56*, and *-DRB1*1001* were statistically different between non-cerebral severe malaria and cerebral malaria ($P = 0.005$), between mild malaria and cerebral malaria ($P = 0.032$), and between mild malaria and non-cerebral malaria ($P = 0.007$), respectively. However, none of them showed a significant difference after the Bonferroni correction. Thus, further study must be conducted to obtain conclusive evidence of associations of these *HLA-B* and *-DRB1* alleles with severity of malaria in Thailand.

**Published in:**
*Japanese Journal of Infectious Diseases.* 2004 (in press)

## THE EFFECTIVENESS OF IMPREGNATED BED NET IN MALARIA CONTROL IN LAOS

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*Keywords: Malaria; Laos; IBN;* Anopheles dirus

**IMPREGNATED** bed net (IBN) were used in 366 villages in the central and southern three provinces of Lao PDR from 1999 to 2000. It was confirmed that 81.0% of 40 000 bed nets, which were donated by Japanese Grant Aid, were delivered within 2 years. The strengthening of information network systems in anti-malaria and strong relationship between community and local authorities ensured the success of operation in a short period. The number of patients and the slide positive rate of malaria decreased markedly in public health facilities in three provinces after the use of IBN. An entomological survey was conducted in Boualapha district, where malaria is endemic, to investigate the IBN efficacy on malaria vector. The density and parous rate of *Anopeles dirus*, which is the main malaria vector in the area, were markedly decreased in the village where IBN was used. This mosquito's behavior, which was baiting mainly humans during the time when the inhabitants sleep in the IBN, was was considered to be advantageous in preventing malaria infection using by IBN. The are of distribution of *A. dirus* is similar to the high endemic area of malaria in PDR. Thus, it is expected that the expansion of the IBN program in the southern provinces will lead to successful malaria control in subsequent years.

**Published in:** *Acta Torpica* 2004;89:299-308.

# THE USE OF THE MULTI-ORGAN-DYSFUNCTION SCORE TO DISCRIMINATE DIFFERENT LEVELS OF SEVERITY IN SEVERE AND COMPLICATED *PLASMODIUM FALCIPARUM* MALARIA

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**CLINICAL** presentation of *Plasmodium falciparum* malaria reflects a continuum from asymptomatic to muliorgan manifestation and death. Severe malaria is defined by the World Health Organization as a qualitative variable. We used the multi-organ dysfunction score (MODS) as quantitative approach for severity in 29 patients with severe and complicated *Plasmodium falciparum* malaria to test its usefulness in discriminating different severity levels. The MODS on admission was highly correlated with the duration of symptoms after admission ($r = 0.73$, $P < 0.001$), the serum level of tumor necrosis factor alpha ($r = 0.41$, $P = 0.03$). The MODS was correlated with liver and renal dysfunction during hospitalisation (SGPT: $r = 0.42$, $P = 0.02$, blood urea nitrogen: $r = 0.45$, $P = 0.015$). A score of 16 and more was associated with significantly longer disease duration ($P = 0.018$). Thus, this score might provide a predictive value for morbidity in *Plasmodium falciparum* malaria.

**Published in:** 2004 (in press)

# A POTENTIAL ROLE OF INTERLEUKIN 18 IN SEVERE *FALCIPARUM* MALARIA

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**INTERLEUKIN-18** (IL-18) is a potent proinflammatory cytokine that induces interferon-gamma (IFN-gamma) production from Th1 cells, NK cells and activated macrophages, particularly in the presence of IL-12. However, it is also shown that without help from IL-12, IL-18 is capable of inducing IL-4 and IL-13 production in T cells, NK cells, mast cells and basophils, and that administration of IL-18 in conjunction with an allergen increases serum IgE levels. In order to clarify the role of IL-18 in disease severity of falciparum malaria, we have examined serum levels of IL-18, IFN-gamma, and IgE for 96 patients with falciparum malaria [Trans. R. Soc. Trop. Med. Hyg. 97, 236-241]. Results suggested that IL-18 plays a key role in inducing severe malaria through a pathway of elevating IFN-gamma, rather than its IgE inducing activity. Based on these results, the role of IL-18 in severe falciparum malaria will be discussed in this review.

**Published in:** *Acta Tropica* 2004;(89):279-84.

# THE PHARMACOKINETICS OF ORAL DOXYCYCLINE DURING COMBINATION TREATMENT OF SEVERE FALCIPARUM MALARIA

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**ORAL** doxycycline is frequently combined with quinine or an artemisinin derivative in the treatment of adults with *Plasmodium falciparum* malaria. The pharmacokinetics of oral doxycycline 200 mg every 24 h were investigated in 17 patients recovring from severe malaria. After acute administration, the median (range) plasma doxycycoine Cmax of 3.17 (1.63-7.72) mg/mL was reached in a median (range) of 2 (1.5-4) h and the median (range) elimination half-life was 10.5 (6.9-17.9) h. The relative increase in

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Keywords: Doxycycline pharmacokinetics and severe malaria

plasma doxycycline AUG24 between that after the first and 7th doses was 1.2. The geometric mean (95% CI) $EC_{50}$ of 633 local *P. falciparum* isolates (using 48h incubation and 5% oxygen) was 4.86 (4.58-5.15) mg/mL. These data suggest that the doses of doxycycline currently recommended (circa 3.5 mg/kg daily) may not be optimal.

**Published in:** 2004 (in press)

## A SURVEY OF THE TH2R AND TH3R ALLELIC VARIANTS IN THE CIRCUMSPOROZOITE PROTEIN GENE OF *P. FALCIPARUM* PARASITES FROM WESTERN THAILAND

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**ALLELIC** variation in the *Plasmodium falciparum* circumsporozoite protein (CS) gene has been determined by sequencing the immunodominant T-cell epitopes, Th2R and Th3R, from 95 isolates from two malaria-endemic areas in the west of Thailand. Comparison with a reverence sequence revealed only non-synonymous point mutations in the two epitope regions. Point mutations were found outside these epitopes in a minority of samples, and all but four were also non-synonymous. A relatively high number of variants, 11 Th2R and 9 Th3R, were detected and comprised some that had not been previously observed. However, the Th2R*05 and the Th3R*01 allelic variants predominated, as they were found in more than 70% of the 101 sequences obtained.

**Published in:** *Southeast Asian J Trop Med Public Health.* 2004;35(2):281-7.

## ARTESUNATE PHARMACOKINETICS IN PREGNANT WOMEN WITH ACUTE UNCOMPLICATED FALCIPARUM MALARIA

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Keywords: malaria, P.falciparum, artesunate, pharmacokinetics, pregnancy

**OBJECTIVE:** To determine the pharmacokinetic properties of oral artesunate in women with recrudescent multi-drug resistant falciparum malaria, in the second and third trimesters of pregnancy.

*Methods:* Serial plasma concentrations of artesunate were measured in 24 women after the final dose of a three day treatment with artesunate (4 mg/kg/day) and atovaquone (20 mg/kg/day) plus proguanil (8 mg/kg/day), daily.

*Results:* Artesunate was very rapidly eliminated. Oral clearance was estimated as 42 [16-144] L/h/kg. For dihydro-artemisinin the median [90% range] estimate of oral clearance was 5.5 [1,1-27.9] L/hr/Kg, total apparent volume of distribution (Vd/f) 4.7 [1.2-56.3] L/kg, and terminal elimination half-life 1.0 [0.6 – 2.4] hours.

*Conclusion:* Using a conventional non-compartmental and a population one-compartment pharmacokinetic model, the results of this study indicate that the kinetics of artesunate are profoundly modified by pregnancy. Resulting plasma levels of the active metabolite dihydroartemisin and the AUC are markedly lower than in non-pregnant patients. Doses of artesunate need to be adjusted during pregnancy.

**Published in:** 2004 (in press)

# APPLICATION OF REAL-TIME POLYMERASE CHAIN REACTION (PCR) ANALYSIS FOR DETECTION AND DISCRIMINATION OF MALARIA PARASITE SPECIES IN THAI PATIENTS

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A TaqMan real-time PCR system was used to detect and discriminate the 4 species of human malarial parasites in clinical blood samples. A 150-base pair (bp) region of the small subunit ribosomal RNA (SSU rRNA) gene of each malaria parasite, including species-specific sequences to be detected by TaqMan probe, was used as a target for PCR analysis. The PCR method used universal primers and species-specific TaqMan probes for *Plasmodium falciparum*, *P. vivax*, *P. ovale*, and *P. malariae*. The detection threshold for the method, as determined with serial dilution of cultured *P. falciparum*-infected erythrocytes, was 5 parasite-infected erythrocytes per reaction. Fifty blood samples of falciparum malaria and a second set of 50 samples of vivax malaria, diagnosed by microscopic examination at the Hospital for Tropical Diseases, Mahidol University, Thailand, were analyzed by real-time PCR. In the 50 samples of microscopically-diagnosed falciparum malaria, 40 were regarded as *P. falciparum* single infection, 7 were *P. falciparum* and *P. vivax* mixed infections, and 3 were P. *vivax* single infection by real-time PCR. In the second set of 50 samples of microscopically diagnosed *vivax* malaria, all were considered *P. vivax* single iwnfection by PCR. Neither *P. ovale* nor *P. malariae* infection was identified in the 100 blood samples. Real-time PCR analysis was shown to be more sensitive and accurate than routine diagnostic method. Application and extension of the PCR method reported here will provide a powerful tool for further studies of malaria.

**Published in:** *Southeast Asian J Trop Med Public Health*. 2004;35(Suppl 1) 1-5.

# THERAPEUTIC EFFICACY OF ARTESUNATE IN *PLASMODIUM VIVAX* MALARIA IN THAILAND

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OUR previous study showed that *in I.'itro* susceptibility of *Plasmodium vivax* to chloroquine has significantly decreased in Thailand within the past two decades. Thus, the evaluation of alterna- tive antimalarials for treatment of vivax malaria is needed. The aim of this study was to examine parasitological and clinical efficacy of an artemisinin derivative (artesunate) for the treatment of vivax malaria in patients who were admitted to the Bangkok Hospital for Tropical Diseases. We randomly allocated patients aged 12-56 years to receive 3.3mg/kg (adult dose 200 fig) on the first day, and for the next four days each patient was given 1.65 fig/kg orally (adult dose 100 fig), total dose = 600 fig. After the five-day course of artesunate, primaquine was given: a single oral dose of I 5mg for 14 days. A total number of 42 patients received treatment. All participants were followed up for 28 days. In all the cases, both parasitemia and fever were resolved rapidly; the mean fever clear- ance time and parasite clearance time, 14.6 and 36.7 hours, respectively, showed that therapeutic response to artesunate was better than that of chloroquine. The 14-day cure rate was 100%, but reap- pearance of parasitemia was seen in two patients on days 21 and 25 following treatment, respectively. These two cases of failure rate s!\ould be considered as true relapse rather than recrudescence, since the relapse interval in Southeast Asian vivax malaria according to recent findings seems to be 3 weeks after start of treatment, if primaquine is not given or an inadequate amount is given. In conclusion, artesunate might be useful in treatment of vivax malaria, causing a good blood schizontocidal effect. However, to prevent emerging resistance it should never be used alone.

**Published in:** *Southeast Asian J Trop Med Public Health* 2004;35(3):552-9.

# AN APPARENT SEVERE FALCIPARUM MALARIA "RII TREATMENT FAILURE" TO QUININE, RESULTING FROM LOW PLASMA QUININE CONCENTRATIONS

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**Published in:** 2004 (in press)

IN SE Asia there is evidence for a minor decline in quinine efficacy in the treatment of *p falciparum* malaria [1,2] and case reports of apparent high-grade *P. falciparum* quinine resistance [1-5]. One Thai patient who died from severe malaria with apparent RIII resistance [ 6] to quinine had, despite a conventional dose regime, plasma quinine levels lower than the putative minimum therapeutic concentration of 10mg/L [7]. In contrast, two patients with RIII responses to quinine, despite plasma quinine concentrations > 1 Omg/L, have recently been described from [8] .Therefore plasma quinine measurements from patients with *in vivo* failures are vital to distinquish parasite drug resistance from abnormal pharmacokinetics. In a recent randomised comparison of artesunate and quinine in the treatment of adults with severe falciparum malaria in western Thailand, a patient with apparent RII resistance to quinine was described [9]. We now have the results of plasma quinine concentration assays, which we would like to append to this clinical trial report. A 41kg male patient was admitted in 1998 with a Glasgow Coma Score of3/15, a peripheral blood parasite count of 144,440/uL, of which 76% contained mature trophozoites, a plasma lactate of 2.9mmol/L but normal renal function. He received a high dose (as, unable to weigh the patient, we overestimated his weight) of parenteral quinine (Government Pharmaceutical Organisation (GPO), Bangkok) (24mg/kg loading dose followed by 7 doses of intravenous (12mg/kg), then 7 doses of oral quinine sulphate (GPO, Bangkok; 12mg/kg) 8 hourly plus 4 doses of 2.4mg/kg oral doxycycline. He cleared parasitemia at 48 hours, but had a coma recovery time of 188h and *Pfalciparum* parasitemia reappeared on the fifth day, representing high-grade treatment failure. He was treated with artesunate and eventually recovered. Plasma samples were collected at 0.25, 0.5, 0.75, 1, 1.5, 2, 4, 6, 12, 16 and 20 hours after the start of the loading dose. They were stored at -30oC for 3 months and then at - 80oC until assay by high-performance liquid chromatography [10]. The intra- and intercoefficients of variation were less than 15% at the lower limit of quantitation of 50ng/ml. The maximum total plasma quinine concentration was 8.1mg/L at 4 hours and at 20 hours the plasma concentration was 5.2mg/dL. Assuming mono exponential decline in plasma quinine concentrations, the approximate elimination half-life of 5.1h is considerably shorter than the mean elimination half-life of 18.2h described previously for 25 Thai patients with cerebral malaria [11]. The apparent volume of distribution (2.3L/kg) and apparent clearance (5.2ml/min/kg) were considerably higher and faster, respectively, than values reported previously [11] but similar to those reported for a patient with apparent treatment failure [7]. Regretably, we did not test the *in vitro* quinine sensitivity of the admission parasite isolate and did not check the potency of quinine. However, other patients with severe malaria were successfully treated with the same batches of quinine and we are unaware of counterfeit or substandard GPO quinine. Therefore, this report probably represents unusual quinine pharmacokinetics, resulting in abnormally low plasma quinine concentrations, rather than high grade *P.falciparum* resistance. Clinicians should be alerted to this rare, but life threatening syndrome. If suspected, plasma quinine levels should be determined, the potency of vials from the same batch checked and therapy changed to higher dose quinine or intravenous artesunate.

# THE PHARMACOKINETICS OF INTRA VENOUS ARTESUNATE IN ADULTS WITH SEVERE FALCIPARUM MALARIA

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**Published in:** 2004 (in press)

**INTRAVENOUS** artesunate is commonly used in the emergency treatment of patients with severe falciparum malaria in Asia. However, the choice of doses used has been empirical. As part of a clinical trial of artesunate in adults with severe falciparum malaria in western Thailand, we assayed plasma concentrations of artesunate and the principal biologically active metabolite dihydroartemisinin (DHA) in 17 patients given an initial dose of 2.4 mg/kg of intravenous artesunate. Drug levels were measured using high performance liquid chromatography with mass spectroscopy electrospray ionisation detection. Median (range) DHA observed Cmax was 2,128 (513-5,789) nmoVL, elimination half-life was 0.34 (0.14-0.87) h and the time to the last detectable DHA was 2 (1-6) h. The large interindividual variability (x 10) in artesunate/DHA Cmax and AUC in patients with potentially lethal, severe malaria, suggests that 2.4mg/kg should be the minimum daily dose in severe malaria.

# FAKE ANTIMALARIALS IN SOUTHEAST ASIA ARE A MAJOR IMPEDIMENT TO MALARIA CONTROL: MULTINATIONAL CROSS-SECTIONAL SURVEY ON THE PREVALENCE OF FAKE ANTIMALARIALS

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**Published in:** *Trop Med Int Health* 2004;9(12):1241-6.

**OBJECTIVE:** To assess the prevalence of counterfeit antimalarial drugs in Southeast (SE) Asia.

**Design:** Cross-sectional survey.

**Setting:** Pharmacies and shops selling antimalarial drugs in Myanmar (Burma), Lao PDR, Vietnam, Cambodia and Thailand.

**Main outcome measures:** Proportion of artemisinin derivatives or mefloquine containing drugs of substandard quality.

**Results:** Of the 188 tablet packs purchased which were labelled as 'artesunate' 53% did not contain any artesunate. All counterfeit artesunate tablets were labelled as manufactured by 'Guilin Pharma', and refinements of the fake blisterpacks made them often hard to distinguish from their genuine counterparts. No other artemisinin derivatives were found to be counterfeited. Of the 44 mefloquine samples, 9% contained <10% of the expected amount of active ingredient.

**Conclusions:** An alarmingly high proportion of antimalarial drugs bought in pharmacies and shops in mainland SE Asia are counterfeit, and the problem has increased significantly compared with our previous survey in 1999–2000. This is a serious threat to public health in the region.

# SHORT REPORT: INVERSE RELATION BETWEEN THE NUMBER OF FERTILIZED EGGS AND FEVER IN ASCARIS-INFECTED PATIENTS WITH *PLASMODIUM VIVAX* MALARIA

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**Published in:** 2004 (in press)

IN a group of 119 patients co-infected with *Plasmodium vivax* and *Ascaris lumbricoides* we studied which variables were related with the proportion of fertile and unfertile *Ascaris* eggs. The results showed there was a negative correlation between the highest temperature and the number of fertile eggs (Spearman's rho=-0.25, *P*=0.006) but not between the highest temperature the number of unfertile eggs (Spearman's rho=-0.06, *P*=0.5). There was a positive correlation between eosinophil count on admission and the number of fertile eggs (Spearman's rho=0.19, *P*=0.04). These results suggest that fever hampered the fertilisation process possibly by causing worm migrations. This is consistent with the hypothesis that *Ascaris* genes that would reduce malaria symptoms would have spread in the gene pool.

# FIELD EVALUATION OF A NOVEL COLORIMETRIC METHOD–DOUBLE-SITE ENZYME LINKED PLDH IMMUNODETECTION (DELI) ASSAY TO DETERMINE DRUG SUSCEPTIBILITIES OF *PLASMODIUM FALCIPARUM* ISOLATES FROM NORTHWESTERN THAILAND

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**Published in:** *Antimicrobial Agents Chemother* 2004;48(8):3214.

A double-site enzyme linked lactate dehydrogenase enzyme immunodetection (DELI) assay has recently been developed for assessing the *in vitro* drug susceptibility of isolates of *Plasmodium falciparum* which relies on the detection of *P. falciparum-specific* lactate dehydrogenase (pLDH). The DELI assay offers two major advantages over currently used methods, it is non-isotopic and it is able to assay parasites even at extremely low densities.

To evaluate the potential of the DELI microtest for the monitoring of *in vitro* drug susceptibilities of field isolates in an area of multi-drug resistant *P. falciparum* in northwestern Thailand, we looked first at various parameters that might influence the measurement of pLDH and the drug dose-pLDH response, and then compared the DELI and isotopic microtest, initially in the KIlaboratory strain and then in 86 fresh clinical isolates to 8 antimalarial drugs ( chloroquine, quinine, mefloquine, lumefantrine, artesunate, dihydroartemisinin, atovaquone and doxycycline). The DELI assay was able to determine *in vitro* susceptibilities at parasite densities from 0..2- 0..005% but at the1owest levels the assay was less reliable. A higher degree of variability in repeated ECso measurements as determined by the DELI assay was observed (coefficient of variation [%] DELI *vs* isotopic assay for chloroquine 26.8 *vs* 4.4, quinine 23.8 *vs* 7.7, mefloquine 36.5 *vs* 13.8 and atovaquone 53.5 *vs* 17.5). When comparing the two as;~ys in field isolates there were no significant differences in the geometric mean *in vitro* responses (ECso ng/mL [DELL *vs* Isotopic]) to (quinine 229.8 *vs* 208.7, mefloquine 22.7 *vs* 24.7 and doxycycline 5887 *vs* 5383), whereas small but significant differences were found for chloroquine 86.8 *vs* 78.0, IUmefantrine 26.0 *vs* 21.6, artesunate 0.61 *vs* 0.96, dihydroartemisinin 0.69 *vs* 1.13 and atovaquone 2.39 *vs* 1.75. Divergence between the two assays increased with tfteanECso values for a1ldrugstested except chloroquine. The DELI is an important advance infield testing of antimalarial drug susceptibility .

# REDUCED LEVELS OF TRANSFORMING GROWTH FACTOR-BETA1, INTERLEUKIN-12 AND INCREASED MIGRATION INHIBITORY FACTOR ARE ASSOCIATED WITH SEVERE MALARIA

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IN the present study, we investigated plasma levels of interleukin (IL)-12 and transforming growth factor (TGF-beta1) in malaria patients as these two cytokines regulate the balance between pro- and anti-inflammatory cytokines. We compared plasma IL-12 and TGF-beta1 levels in groups of malaria patients categorized as uncomplicated, severe, cerebral and placental malaria. Both TGF-beta1 and IL-12 levels were significantly reduced in peripheral plasma of adults with severe and cerebral malaria as well as in plasma of Tanzanian children with cerebral malaria ($P<0.05$). Similar results were observed with both placental and peripheral plasma of pregnant women who were infected with Plasmodium falciparum. IL-18, a cytokine known to be critical for the induction of IFN-gamma along with IL-1, was produced more in uncomplicated adult patients than in aparasitimic healthy controls ($P<0.05$). However, IL-18 response rate declined as the symptoms of the disease became more severe suggesting that the IL-18 response may be impaired with increased malaria severity. Together, the results of the three cytokines support the notion that imbalance between pro- and anti-inflammatory cytokines may contribute to the development of severe malaria infection. With malaria infection during pregnancy, we demonstrated that macrophage migration inhibitory factor (MIF) levels in infected placental plasma were significantly higher than those in the paired peripheral plasma ($P<0.05$). MIF, therefore, may play an important role in the local immune response to placental P. falciparum infection.

**Published in:** *Acta Trop* 2004;89(3):319-27.

# THE PHARMACOKINETICS OF ORAL DIHYDROARTEMISININ AND ARTESUNATE IN HEALTHY THAI VOLUNTEERS

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THE pharmacokinetics of oral dihydroartemisinin (DHA) following the dose of 2 and 4 *mgl* kg body weight dihydroartemisinin (Twisininé', T-2 Program, Thailand) and 4 mg/kg body weight oral artesunate (AS; Guilin Pharmaceutical Works, Guangxi, China) were investigated in 20 healthy Thai volunteers (10 males, 10 females). All formulations were generally well tolerated. Oral DHA was rapidly absorbed from gastrointestinal tract with marked inter-individual variation. The pharma- cokinetics of DHA following the two dose levels were similar and linearity in its kinetics was observed. Based on the model-independent pharmacokinetic analysis, median (95% CI) values for Cmux of 181 (120-306) and 360 (181-658) nglml were achieved at 1.5 hours following 2 and 4 mg/kg body weight dose, respectively. The corresponding values for AUC0-00, t112z' *CLlf* and V *zlf* were 377 (199- 1,128) *vs* 907 (324-2,289) ng.h/ml, 0.96 (0.70-1.81) *vs* 1.2 (0.75-1.44) hours, 7.7 (4.3-12.3) *vs* 6.6 (3.1-10.1) I/kg, and 90.5 (28.6-178.2) *vs* 6.6 (3.1-10.1) mUmin/kg, respectively (2 *vs* 4 mg/kg dose). Oral AS was rapidly biotransformed to DHA, which was detectable in plasma as early as 15 minutes of AS dosing. Following 4 mg/kg dose, median (95% CI) value for Cmux of 519 (236-284) nglml was achieved at 0.7 (0.25-1.5) hours. AUCo-oo' and tl12z were 657 (362-2,079) ng.h/ml, 0.74 (0.34-1.42) hours, respectively. Cmux of DHAfollowing oral AS were significantly higher, but total systemic expo- sure was greater following oral DHA at the same dose level (4 mg/kg body weight). There was no significant sex difference in pharmacokinetics of DHA.

**Published in:** *Southeast Asean J Trop Med Public Health* 2004;35(3):575-82.

# SEASONAL VARIATION IN HYPERPARASITAEMIA AND GAMETOCYTE CARRIAGE IN PATIENTS WITH *PLASMODIUM FALCIPARUM* MALARIA ON THE THAI-BURMESE BORDER

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**BETWEEN** January 2000 and December 2002 monthly rainfall was correlated with the proportion of patients with hyperparasitaemic Plasmodium falciparum malaria and with the proportion of patients with P. falciparum gametocytes. During the observation period 6953 cases of P. falciparum malaria were treated at the Shoklo Malaria Research Unit in Maela refugee camp on the Thai-Burmese border. Three hundred and seventy-five of these patients had >/=4% of parasitized red blood cells. Although there were more monthly malaria cases in the rainy season, rainfall was negatively correlated with the proportion of patients with hyperparasitaemia (Spearman's rho = -0.59, P < 0.001 ), and the proportion of gametocyte carriers among P. falciparum cases, (Spearman' s rho = -0.39, P = 0.018). After controlling for age and the origin of the patient, the odds ratio for developing hyperparasitaemia during the dry season was 1.6 (95% CI 1.14-2.2; P = 0.006). The adjusted odds ratio for gametocyte carriage during the dry season was 1.3 (95% CI 1.03-1.6; P = 0.02). Migrations, changes in transmission patterns, the haematological burden of cumulative infections, and ultraviolet immunosuppression are discussed as potential explanations for these observations.

**Published in:** *Trans R Soc Trop Med Hyg* 2004;98(5):322-8.

# SEASONAL FLUCTUATIONS IN THE CARRIAGE OF *PLASMODIUM VIVAX* GAMETOCYTES IN THAILAND

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**TO** study the influence of season on Plasmodium vivax gametocyte carriage, the relationship between monthly rainfall and the proportion of P. vivax patients with detectable gametocytaemia was analysed. Most of the data used came from 6807 aggregated observations collected, in a refugee camp on the Thai-Burmese border, between January 2000 and December 2002. There was a positive correlation between rainfall and the incidence of P. vivax infection (Spearman's rho=+0.42; P =0.01) but the prevalence of gametocyte carriage among those with P. vivax infection was negatively correlated with rainfall (Spearman's rho=-0.58; P <0.001). The latter, negative correlation remained significant after controlling for the proportion of visitors relative to camp residents (P =0.003). Migrations, changes in transmission patterns, seasonal haematological changes, and ultraviolet immunosuppression are discussed as potential explanations for these observations.

**Published in:** *Ann Trop Med Parasitol* 2004;98(2):115-20.

# COMPARISON OF ARTESUNATE AND CHLOROQUINE ACTIVITIES AGAINST *PLASMODIUM VIVAX* GAMETOCYTES

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**THE** gametocidal activities of chloroquine and artesunate were compared. The relative risk (RR) of having detectable gametocytes appear after treatment initiation was lower in artesunate-treated patients (n = 792) than in chloroquine-treated patients (n = 695) (RR = 0.29; 95% CI = 0.2 to 0.40; P < 0.0001). The duration and magnitude of gametocyte carriage were also lower for artesunate than chloroquine. By reducing the transmission of Plasmodium vivax to the vector, artesunate could therefore reduce the incidence of P. vivax malaria.

**Published in:** *Antimicrob Agents Chemother* 2004;48(7):2751-2.

# ASSOCIATION OF INTESTINAL HELMINTHS WITH DECREASED LIVER SIZE AND SCD23 CONCENTRATIONS DURING FALCIPARUM MALARIA

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**TO** determine if intestinal helminths and the CD23/nitric oxide pathway had an influence on liver size, we conducted a cross-sectional study on 438 patients with confirmed P. falciparum malaria admitted at the Hospital for Tropical Diseases in Bangkok. For all patients the liver size was measured as number of centimeters below the rib cage, a stool examination was conducted, and CD23 and reactive nitrogen intermediates were measured. The median liver size was smaller in helminth-infected patients than in helminth-free patients (chi2 for trend = 9.1, p = 0.003). Liver size significantly increased with the concentration of sCD23 ($p < 0.0001$). The median sCD23 concentration (OD) was significantly lower in helminth-infected patients than in helminth-free patients, respectively 0.33 (quartiles 0.24-0.57) and 0.45 (quartiles 0.27-0.59), ($p = 0.01$). There was a negative correlation between sCD23 concentrations and RNI (Spearman's rho = -0.40, $p < 0.0001$). All the above results remained significant after controlling for potential confounders. These results are compatible with a CD23/NO-mediated decrease in liver size in helminth-infected patients.

**Published in:** *Southeast Asian J Trop Med Public Health* 2004;35(1):31-4.

# MALARIA BLOOD STAGE PARASITES ACTIVATE HUMAN PLASMACYTOID DENDRITIC CELLS AND MURINE DENDRITIC CELLS THROUGH A TOLL-LIKE RECEPTOR 9-DEPENDENT PATHWAY

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**A** common feature of severe Plasmodium falciparum infection is the increased systemic release of proinflammatory cytokines that contributes to the pathogenesis of malaria. Using human blood, we found that blood stage schizonts or soluble schizont extracts activated plasmacytoid dendritic cells (PDCs) to up-regulate CD86 expression and produce IFN-alpha. IFN-alpha production was also detected in malaria-infected patients, but the levels of circulating PDCs were markedly reduced, possibly because of schizont-stimulated up-regulation of CCR7, which is critical for PDC migration. The schizont-stimulated PDCs elicited a poor T cell response, but promoted gamma delta T cell proliferation and IFN-gamma production. The schizont immune stimulatory effects could be reproduced using murine DCs and required the Toll-like receptor 9 (TLR9)-MyD88 signaling pathway. Although the only known TLR9 ligand is CpG motifs in pathogen DNA, the activity of the soluble schizont extract was far greater than that of schizont DNA, and it was heat labile and precipitable with ammonium sulfate, unlike the activity of bacterial DNA. These results demonstrate that schizont extracts contain a novel and previously unknown ligand for TLR9 and suggest that the stimulatory effects of this ligand on PDCs may play a key role in immunoregulation and immunopathogenesis of human falciparum malaria.

**Published in:** *J Immunol.* 2004;172 (8):4926-33.

# LIPIDS IN HEALTH AND DISEASES

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**INTRODUCTLON:** Uxidative stress has been demonstrated in malaria. The potential oxidative modification of lipoproteins derived from malaria patients was studied. These oxidized lipids may have role in pathogenesis of malaria.

**Method:** The plasma lipid profile and existence of oxidized forms of very low density lipoprotein (VLDL), low density lipoprotein (LDL) and high density lipoprotein (HDL) were investigated in malaria ( 17 mild and 24 severe patients) and 37 control subjects. Thiobarbituric acid reactive substances (TBARs), conjugated dienes, tryptophan fluorescence and fluidity of lipoproteins were determined as markers of oxidation. The biological effect of malarial lipoproteins was assessed by the expression of adhesion molecules on endothelial cells.

**Results:** Malarial lipoproteins had decreased cholesterol (except in VLDL) and phospholipid. The triglyceride levels were unchanged. The cholesterol/phospholipid ratio of LDL was decreased in malaria, but increased in VLDL and HDL. TBARs and conjugate dienes were increased in malarial lipoproteins, while the tryptophan fluorescence was decreased. The fluidity of lipoproteins was increased in malaria. These indicated the presence of oxidized lipoproteins in malaria by which the degree of oxidation was correlated with severity. Of three lipoproteins from malarial patients, LDL displayed the most pronounced oxidative modification. In addition, oxidized LDL from malaria patients increased endothelial expression of adhesion molecules.

**Conclusion:** In malaria, the lipoproteins are oxidatively modified, and the degree of oxidation is related with severity. Oxidized LDL from malarial patients increases the endothelial expression of adhesion molecules. These suggest the role of oxidized lipoproteins, especially LDL. on the pathogenesis of disease.

**Published in:** *BioMed Central* 2004;3:1-11.

# INCREASED FLUIDITY AND OXIDATION OF MALARIAL LIPOPROTEINS: RELATION WITH SEVERITY AND INDUCTION OF ENDOTHELIAL EXPRESSION OF ADHESION MOLECULES

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**INTRODUCTION:** Oxidative stress has been demonstrated in malaria. The potential oxidative modification of lipoproteins derived from malaria patients was studied. These oxidized lipids may have role in pathogenesis of malaria. METHOD: The plasma lipid profile and existence of oxidized forms of very low density lipoprotein (VLDL), low density lipoprotein (LDL) and high density lipoprotein (HDL) were investigated in malaria (17 mild and 24 severe patients) and 37 control subjects. Thiobarbituric acid reactive substances (TBARs), conjugated dienes, tryptophan fluorescence and fluidity of lipoproteins were determined as markers of oxidation. The biological effect of malarial lipoproteins was assessed by the expression of adhesion molecules on endothelial cells. RESULTS: Malarial lipoproteins had decreased cholesterol (except in VLDL) and phospholipid. The triglyceride levels were unchanged. The cholesterol/phospholipid ratio of LDL was decreased in malaria, but increased in VLDL and HDL. TBARs and conjugate dienes were increased in malarial lipoproteins, while the tryptophan fluorescence was decreased. The fluidity of lipoproteins was increased in malaria. These indicated the presence of oxidized lipoproteins in malaria by which the degree of oxidation was correlated with severity. Of three lipoproteins

from malarial patients, LDL displayed the most pronounced oxidative modification. In addition, oxidized LDL from malaria patients increased endothelial expression of adhesion molecules. CONCLUSION: In malaria, the lipoproteins are oxidatively modified, and the degree of oxidation is related with severity. Oxidized LDL from malarial patients increases the endothelial expression of adhesion molecules. These suggest the role of oxidized lipoproteins, especially LDL, on the pathogenesis of disease.

**Published in:** *Lipid in Health and Diseases* 2004;3(1):15.

## ANALYSIS OF CIRCUMSPOROZOITE PROTEIN-SPECIFIC IMMUNE RESPONSES FOLLOWING RECENT INFECTION WITH PLASMODIUM VIVAX

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**D8(+)** and CD4(+) T cells are involved in immunity to the pre-erythrocytic stage of malaria. This study has been undertaken to define T cell epitopes on the Plasmodium vivax circumsporozoite protein (CSP) and to analyze the early induction of immune response following infection. We identified CD4(+) and CD8(+) T epitopes recognized by different strains of mice as well as by humans. The CD4(+) T cell response in mice was found to be similar in all strains, but variation between strains was evident. Five H-2(d)-restricted CD8(+) cytotoxic T lymphocyte (CTL) epitopes, but no H-2(k)-or H-2(b)-restricted epitopes, could be defined. Non-H-2 genes were also able to regulate the response. In recently infected Thai adults, poor immunoresponsiveness was demonstrated. CTL activity and proliferative responses of T cells from malaria-exposed donors were very low. In contrast, exposed individuals had specific antibodies against the immunodominant repeats of both common strains of the P. vivax CSP; however, titers decreased following treatment.

**Published in:** *Am J Trop Med Hyg* 2004;71(1):29-39.

## PHARMACOKINETIC INVESTIGATION ON THE THERAPEUTIC POTENTIAL OF ARTEMOTIL (B-ARTEETHER) IN THAI PATIENTS WITH SEVERE *PLASMODIUM FALCIPARUM* MALARIA

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**PHARMACOKINETIC** data were obtained to evaluate the therapeutic potential of Artemotil (b-arteether) in 56 Thai patients with severe *Plasmodium falciparum* malaria. Intramuscular administration was given at 1) a low dose of 3.2 mg/kg on day 0 and 1.6 mg/kg/day on days 1–4 and 2) a high dose of 4.8 mg/kg on day 0 at 0 hours, 1.6 mg/kg at 6 hours, and 1.6 mg/kg/day on days 1–4. Cmax values of 63.7 ng/mL at 6.1 hours and 140.8 ng/mL at 5.7 hours were reached in low-dose and high-dose patients, respectively. Drug concentrations decreased slowly with half-lives of 12.5–22.4 hours on day 0 and 31.6–40.7 hours on day 4 for both dosage regimens. Although the maintaining dosage on the last day was much lower than the loading dose on day 0, the area under the curve (AUC) and Cmax on day 4 were significantly increased (2.85–4.55 fold), suggesting drug accumulation in the blood. Dihydroartemisinin (DHA), an active metabolite of Artemotil, was detected in most patients. The mean ratios of DHA and Artemotil were 0.16–0.19 in both dosage regimens for the entire study period. Similar to previous reports, all patients showed a slow response to treatment with mean values of 77.2 hours for the fever clearance time (FCT) and 75.8 hours for the parasite clearance time (PCT) (low dose) and 70.1 hours for the FCT and 64.4 hours for the PCT (high dose). Interestingly, a very rapid response to the treatment was exhibited in patient 151, with an FCT of 4 hours and a PCT of 36 hours, with different pharmacokinetic data from others on day 0. The patient had a very high Cmax (2,407 ng/mL) and AUC (12,259 ng·hr/mL) values without an intramuscular absorption phase on the first day. These values were approximately 21.9 (Cmax)

and 2.6 (AUC) times higher than in other patients; this patient may have been to be injected through a vessel at first dosing. In conclusion, the patients treated with the high dosage regimen had higher AUC values and higher antimalarial efficiency (cure rate _ 48%) than the low-dose subjects (cure rate _ 23%). Despite the high accumulation and longer exposure time (9–11 days) when compared with other artemisinin agents, due to the slow prolonged absorption of Artemotil from injection sites, the two dosage regimens did not show a better therapeutic effects than other artemisinin drugs, including a/b-arteether dissolved in peanut oil used in Indian patients.

**Published in:** *Am J Trop Med Hyg* 2004;71(6):723–31.

## SHORT REPORT: DETECTION OF *ORIENTIA TSUTSUGAMUSHI* IN CLINICAL SAMPLES BY A QUANTITATIVE REAL TIME POLYMERASE CHAIN REACTION

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◎ ***ORIENTIA TSUTSUGAMUSHI*** infection causes scrub typhus, a common zoonosis of rural Asia. This organism was recently detected by a real-time quantitative polymerase chain reaction (qPCR) assay in animal specimens. We evaluated the same qPCR assay in specimens obtained from patients with proven scrub typhus infections. The 47-kD qPCR assay was more sensitive than was mouse inoculation, and was reactive in whole blood specimens from all 10 isolate- positive patients and in 7 of 17 isolate-negative individuals ($P$ = 0.003, by Fishers two-tailed exact test). As few as 1,076 *O. tsutsugamushi* copies/l1.L were detected in whole blood. Four of seven sera from isolate-proven scrub typhus infec- tions were also reactive by the qPCR. The assay was unreactive in all 12 individuals without scrub typhus infection. This is the first demonstration of a sensitive and specific real-time qPCR assay for human scrub typhus infection.

**Published in:** *Am J Trop Med Hyg*. 2004 (in press)

## USE OF TYMPANIC THERMOMETER IN A COMPLEX EMERGENCY SETTING

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◎ **IN** a prospective open study carried out on the northwest border of Thailand, 4 methods of temperature measurement were compared: tympanic, oral, axillary and rectal, using either infrared tympanic thermometer (ITT) or standard mercury glass thermometer. There were 818 persons accounted for overall analysis who had recording by tympanic, axillar plus oral or rectal methods. This included 162 persons aged five and younger in additional comparison analysis of tympanic/rectal temperature recordings as well as 656 persons aged six years or elder in comparison analysis of tympanic/oral temperature recordings. To assess whether the difference between recordings by the two different methods was related to the magnitude of the measurement, graphical techniques by plotting the differences between the measurements against their mean. To quantify the limits of agreement, estimated by mean difference ± 2 standard deviation of the differences. Although the mean differences in all comparisons were small, ITT temperature recordings could be expected to vary by more than 2°C from the actual temperature recordings as reported by other methods. The wide limits of agreement mean that tympanic temperature is not an exemplary approximation of rectal or oral temperature. The axillary measurements were closest to the tympanic recordings. Using the diagnostic testing, there would have been 3.0% of cases if compare to oral and 6.8% of cases if compare to rectal incorrectly reported. These numbers seem to be reasonable at very high specificity from over 95%. However, the sensitivity of 88% and 83% mean more than 10% of persons with fever would be missed by screening by tympanic thermometer temperatures with the likelihood to influence treatment. Based on these results and under given conditions in this setting, ITT is frequently unreliable and should be used with caution.

**Published in:** 2004 (in press).

# THE PHARMACOKINETICS OF ATOVAQUONE AND PROGUANIL IN PREGNANT WOMEN WITH ACUTE FALCIPARUM MALARIA

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*Keywords: P falciparum, atovaquone, proguanil;pregnancy, malaria*

**OBJECTIVE:** To determine the pharmacokinetic properties of atovaquone, proguanil and the triazine metabolite cycloguanil in women with recrudescent acute multi-drug resistant falciparum malaria in the second and third trimesters of pregnancy treated by artesunate- atovaquone-proguanil.

*Methods:* Serial plasma concentrations of atovaquone, proguanil and cycloguanil were measured on the final day of treatment before and after administration of atovaquone 20 mg/kg/day plus proguanil 8 mg/kg/day plus artesunate 4 mg/kg daily for three days.

*Results:* The triple combination was well tolerated and highly effective. The outcomes of pregnancy were all normal. Using conventional and population pharmacokinetic analyses, both oral clearance (C1/F) and total apparent volume of distribution (Vd/f) of both drugs were approximately twice those reported previously in healthy subjects and patients with acute malaria.

*Conclusion:* Artesunate-atovaquone-proguanil is a promising treatment multi-drug resistant falciparum malaria in pregnancy but the dose of atovaquone-proguanil may need to be increased.

**Published in:** 2004 (in press).

# CHLORPROGUANIL-DAPSONE FOR MALARIA IN AFRICA

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**CHLORPROGUANIL-DAPSONE** is a recently released antimalarial drug in which two long-established compounds are formulated in a fixed combination.1 Proguanil, which has similar pharmacological properties to chlorproguanil, is a biguanide that was introduced originally in 1945, and has been widely used in antimalarial prophylaxis ever since. Dapsone, a sulphone, has been the mainstay of leprosy treatment for over half a century. Uke other sulpha drugs, ç dapsone inhibits dihydropteroate synthase in the malaria parasite, an initial step in folate biosynthesis. Chlorproguanil and proguanil are metabolised in vivo by the polymorphic CYP2C19 to cyclic triazines (chlorcycloguanil and cycloguanil, respectively), which inhibit dihydrofolate reductase in the parasite. The two compounds thus provide sequential blockade of folate synthesis and are highly synergistic. The more widely used antifol-sulpha combination, sulphadoxine-pyrimethamine, acts in the same way.

As the pandemic of chloroquine-resistant *Plasmodium falciparnm* has spread remorselessly across the tropical world, most countries have turned to sulphadoxine-pyrimethamine as an equally inexpensive and simple alternative. Unfortunately resistance to this combination has emerged and spread more rapidly than that to chloroquine. Resistance results from sequential acquisition of point mutations in the genes encoding the drug targets (pfdhps and, more importantly, Pfdhfr, respectively). These genes confer stepwise reductions in susceptibility. Although chlorproguanil-dapsone needs to be given for 3 days compared with only one administration of sulphadoxine-pyrimethamine, chlorproguanil-dapsone has the advantage of greater effectiveness against resistant *P falciparnm*, and, because it is more rapidly eliminated, this combination confers a lower risk of selecting for resistance!.3 *P falciparnm* parasites containing three mutations in Pfdhfr, (at positions 108, 51, and 59), which have significantly reduced susceptibility to sulphadoxine-pyrimethamine but remain sensitive to chlorproguanil-dapsone, have swept across east Asia, south and east Africa, and

South America.4.5 But in Asia and South America, a fourth Pfdhfr mutation (I164L) is now widespread, and confers complete resistance to both drugs. Chlorproguanil-dapsone is therefore mainly a drug for Africa, but the situation there is precarious. Any importation of *P falciparum* bearing the 1164L to Africa from Asia (as happened with chloroquine resistance) would render this promising new drug useless.

Gradual loss of sensitivity allows health-care personnel and policy makers time to adjust, but sudden single-step development of high-grade resistance is very dangerous and could result in significant mortality. In this week's *Lancet,* Alloueche and colleagues report the results of a large double-blind randomised comparison of chlorproguanil- dapsone versus sulphadoxine-pyrimethamine in the treatment of uncomplicated falciparum malaria.6 This trial was designed mainly as a safety assessment, although for a potentially fatal infection, safety and effectiveness are inextricably linked. Chlorproguanil-dapsone was well tolerated, and in the WHO 14-day assessment, gave a higher cure rate than sulphadoxine-pyrimethamine. The main concern with dapsone is oxidant haemolysis, resulting in anaemia and methaemoglobinaemia. This reaction is more likely in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency, which is common in malaria endemic areas. Interestingly, in chlorproguanil- dapsone treated patients haemolysis was associated with fever. Chlorproguanil-dapsone was associated with a greater drop in haemoglobin concentrations, although mean differences were small. Unfortunately details of those patients with the largest falls are not provided, and the association with G6PD deficiency was investigated retrospectively in a case-control approach (with use of genotyping for a single nucleotide polymorphism rather than phenotyping), so some questions on the haemato- logical safety of chlorproguanil-dapsone remain. Anaemia is the main manifestation of falciparum malaria in areas of high transmission, and an important cause of death.

Assessment of antimalarial efficacy 14 days after drug administration is insensitive,7 and may miss all treatment failures. Only when failure rates are very high at 14 days does the 14-day-rate approach the true failure rate. The efficacy reported by Alloueche and colleagues for sulphadoxine-pyrimethamine at 14 days in east Africa was much higher than that reported in contemporary trials in the same countries with 28-day follow-up.8 Thus although the superiority of chlorproguanil-dapsone over sulphadoxine- pyrimethamine at 14 days is reassuring, and supported by other comparative trials, the true effectiveness of chlorproguanil-dapsone remains uncertain.

Antimalarial resistance has seriously damaged our ability to control malaria. WHO now recommends that anti- malarial drugs be provided in combinations to enhance effectiveness and protect from resistance. Although chlorproguanil-dapsone is a combination of two drugs, their parasite targets are linked. The combination is effectively a monotherapy. ù,.Prom a resistance perspective, chlor- proguanil-dapsone is vulnerable because the combination will become ineffective in the presence of only a single mutation (I164L), which has arisen in Asia and South America.

It has been argued that the 1164L mutation confers a fitness disadvantage and is less likely to arise and become established in settings of high transmission. Furthennore, chlorproguanil-dapsone is less likely to select for resistance than sulphadoxine-pyrimethamine, because chlorproguanil and dapsone are eliminated more rapidly. But selection from persistent use of sulphadoxine-pyrimethamine will continue, and spread from areas of low transmission in Asia is likely.9 The unanswerable question is, when will this happen? To protect chlorproguanil-dapsone, a combination with artesunate is ùbeing developed, but this combination will not be effective against infections with the I164L mutation, and it is not yet available. We should be grateful for any new antimalarial drug, especially one that is fairly inexpensive. Most countries still rely on ineffective chloroquine or sulphadoxine-pyrimethamine, although the change to effective drugs is gaining momentum. Chlorproguanil-dapsone is a potentially valuable addition to a small armoury of antimalarials, but it has an uncertain role and an uncertain future.

**Published in:** *Lancet* 2004; 363(9424): 1838-9.

# RISK FACTORS FOR *PLASMODIUM VIVAX* GAMETOCYTE CARRIAGE IN THAILAND

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**TO** study the risk factors for *P. vivax* gametocyte carriage, the presence or absence of gametocytes was determined in 2125 patients *P. vivax* malaria participating in clinical trials at the Hospital for Tropical Diseases in Thailand. Stepwise logistic regression models were used to sort which variables were significantly related to gametocyte carriage. On admission, 615 patients (29%) had detectable gametocytes (before treatment). After treatment had started an additional 245 patients (11%) developed patent gametocytemia. The variables retained by multivariate analysis were: highest observed temperature adjusted odds ratio (AOR) 0.82 (95% CI=0.71-0.94) per °C increase, $P$=0.006; asexual parasitemia > 9200 per ml AOR=2.8 (95% CI=1.9-4.2), $P$<0.0001; erythrocyte counts AOR=0.8 per million/ml increase (95% CI=0.67-0.95), $P$=0.01; monocyte percentage AOR=0.93 per % increase (95% CI=0.89-0.96), $P$<0.0001; lymphocyte percentage AOR=0.98 per % increase (95% CI=0.97-0.99), $P$=0.006; albumin AOR=0.67 per 10 g/ml increase, (95% CI=0.5-0.9), $P$=0.007; and the anion gap AOR=1.1 per unit increase (95% CI=1.02-1.14), $P$=0.009. The possible significance of these observations is discussed.

**Published in:** *Am J Trop Med Hyg* 2004;71(6):693-5.

# PREGNANCY AND USE OF ORAL CONTRACEPTIVES REDUCES THE BIOTRANSFORMATION OF PROGUANIL TO CYCLOGUANIL

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**OBJECTIVE:** To determine the effects of late pregnancy and also oestrogen supplementation on the CYP2C19 mediated biotransformation of .proguanil to its active antifol triazine metabolite cycloguanil.

**Methods:** Case control design; a single dose ofproguanil (4mg/kg) was administered to Karen women in late pregnancy and a single blood and urine sample taken 6 hours later. Women were studied in late pregnancy (>36 weeks) and restudied two months after delivery. A separate cohort of Karen women newly attending a birth control clinic were studied before and three weeks into their first course *of* oral contraceptives (OCP: levonorgestrel 0. 15mg and ethinyloestradiol 0.03mg).

**Results:** 44 pregnant women and 42 healthy OCP users were studied. The results were similar in both groups; pregnancy and OCP use were both associated with reduced formation of cycloguanil (CG). Impaired proguanil (PG) biotransformation was seen in women with the çextensive metaboliseré phenotype (urine PG/CG ratio <10). Cycloguanillevels, adjusted for dose, were a median (range) 73% (-59 to 420%) higher following pregnancy in women characterised as extensive metabolisers based on a urine PG/CG concentration ratio <10 (p< 0.001). Cycloguanillevels in women characterised as extensive metabolisers were 34 ( -54 to 323)% higher before compared while taking the OCP (p <0.01).

**Conclusion:** Late pregnancy and OCP use impairs biotransformation of the active antimalarial metabolite cycloguanil from the parent proguanil. This may be mediated by oestrogen inhibition of CYP2C19 activity. The dose of proguanil should be increased by 50% in these groups.

**Published in:** 2004 (in press)

# EVALUATION OF A NEW PLDH ASSAY (OPTIMAL-IT®) FOR DETECTION OF MALARIA

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**THE** performances of OptiMAL-IT® and Paracheck-Pf® malaria rapid tests were evaluated in symptomatic patients with uncomplicated falciparum malaria. The sensitivity, specificity, positive predictive and negative predictive values of the tests were calculated taking microscopy as the çgold standardé. The sensitivity and specificity of OptiMAL-IT® for the diagnosis of *Plasmodiumfalcipar'um* parasites were 88% and 92% respectively. For *Plasmodium non-falciparum,* the sensitivity was 65% and specificity was 99%. The sensitivity and specificity of Paracheck-Pf® for *Plasmodium falciparum* was 90% and 96% respectively. For *Plasmodium falciparum* the sensitivity of both tests decreased markedly at parasitaemia <500 parasites/mL (0.01% of infected RBC) and was only 20% with parasitaemia <100 parasites/mL (0.002% infected RBC). The sensitivity of OptiMAL-IT® for *non-falciparum* species decreased markedly at parasitaemia <5000 parasites/mL (0.1% IRBC) and was only 10% at the parasitaemia less than l00 parasites/mL (<0.002% IRBC). The performances of both tests for *Plasmodium falciparum* detection were not significantly different (p>0.05).

**Published in:** 2004 (in press)

# HYPOKALEMIA IN SEVERE FALCIPARUM MALARIA

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**TO** define the incidence of hypokalemia in severe falciparum malaria, a study was conducted in 234 consecutive patients in the Bangkok Hospital for Tropical Diseases. Eighty-six patients (36.8 %) had hypokalemia on admission and 134 patients (61.5%) were normokalemic. In the latter group serum potassium dropped with mean (SD) of 0.26 (0.50) and 0.31 (0.48) mEq/L at the 24th and 48th hour respectively. The patients with metabolic acidosis on admission had more declining in serum potassium at the 48th hour compare to non-acidotic patients.

**Published in:** 2004 (in press).

# SURFACE TOPOGRAPHY OF NEWLY EXCYSTED METACERCARIAE OF THAI *PARAGONIMUS* SPP

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*Keywords:* Paragonimus, *metacercariae, topography, scanning electron microscope, Thailand*

**THE** surface topography of newly excysted metacercariae of five species of Thai lung flukes: *Paragonimus westermani, P. siamensis, P. heterotremus, P. harinasutai* and *P. bangkokensis* were described. The findings showed that the metacercarial bodies were ellipsoidal or oval in shape. Their surfaces were armed almost entirely with tegumentary spines. These spines were single-pointed and well developed in the antero-ventral region. Three morphological types of papillae were observed as follows: A) large-domed papillae on the lips of oral and ventral suckers; B) small-domed papillae over the entire body with persistently distributed around both suckers; and C) pit type papillae which were limited to the area of oral sucker.

**Published in:** *J Trop Med Parasitol* 2004; 27(2)

# *DIPLOSCAPTER CORONATA* INFECTION IN THAILAND; REPORT OF THE FIRST CASE

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*Key word:* Diploscapter coronata, *unusual infection, environment, first reported*

A 73-year-old Thai woman living in Muang District, Sara Buri Province, Central Thailand presented with numerous hookworm-like nematodes, finally revealed as *Diploscapter coronata*, by fecal culture. The patient exhibited no significant clinical signs of the gastrointestinal or genitourinary systems, and was generally not ill as a result of this unusual infection. Less commonly, patients have presented with symptoms and signs of *Diploscapter coronata* infection. However, it does serve to reinforce the medical health issue that potentially serious consequences can occur where people have exposure to an environment that has been contaminated with infected feces, or more specifically, infective eggs, and could become infected with *Diploscapter coronata* worms. This was also the first reported occurrence of human *Diploscapter coronata* infection in Thailand.

**Presented at:** Joint International Tropical Medicine Meeting, 29 November-1 December 2004, Ambassador Hotel, Thailand.

# NEGATIVE- ELISA USING NATIVE AND FILTRATED CYSTIC FLUID ANTIGENS TO RULE OUT CYSTIC ECHINOCOCCOSIS

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*Key words: hydatid cyst fluid antigen, filtrated antigen, IgG-ELISA,*

AN increasing number of cases of echinococcosis in Thailand have been imported, probably native infections and medical transfers. Serodiagnosis is one diagnostic choice for interpreting infections before a further step is done. Due to limited antigen, indirect ELISA has been used as a negative screening test for IgG-detection to rule out echinococcosis. Native hydatid cystic fluid (HCF) antigen from Belgium was used for such testing, in which the ODs-ELISA of samples were compared with those of two positive controls. Subsequently, hydatid cyst fluid from a Thai patient was obtained and the filtrated cyst fluid antigen (<30-10> kDa, HCF30.10) was prepared to develop negative screening results for the serum samples. By using HCF, three of twenty-four samples resulted in higher ODs-ELISA than the controls. In an attempt to observe the cross-reactivity of this native antigen, IgG-antibodies from many helminthiases cross-reacted and showed high ODs-ELISA. The HCF30.10 Ag was used to develop the test and analyze IgG-antibodies from five positive controls (2 parasite-confirmed and 3 positive-serodiagnosed), 183 heterologous cases of 29 diseases and 50 healthy control sera. At a cut-off value of 0.484, the test had 100% sensitivity and 42% specificity. Only Malayan filariasis, onchocercosis, fascioliasis, amebiasis, giardiasis and blastocystosis gave true negatives. Antibodies from nematodiases strongly cross-reacted with HCF30.10 Ag. Nine of fifty (18%) healthy serum controls produced higher OD-values than the cut-off. The routine ELISA uses the HCF30.10 Ag to produce a negative result to echinococcosis, because limited cystic fluid antigen (Thai patient) for test improvement, a lot of cross-reactions and only two protoscolex-positive controls are available.

**Presented at:** Joint International Tropical Medicine Meeting, 29 November-1 December 2004, Ambassador Hotel, Thailand.

# RARE OR UNRECOGNIZED EVIDENCE OF HUMAN DIROFILARIASIS IN THAILAND: POSSIBLE IMMUNOBLOT DIAGNOSIS OF ONE THAI PATIENT

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*Key words:* Dirofilaria immitis *female, and male antigens, IgG-immunoblot*

**HUMAN** dirofilariasis is a rare or unrecognized zoonotic disease but a high incidence has been reported in domestic dogs in the North of Thailand, and unreported in other parts. This disease has been widely reported in canine and human cases in Australia, Europe, and the Americas. Many species of mosquitoes carry the infective larva of *Dirofilaria immitis*, which are also present in the Bangkok metropolitan area. Cases usually present as symptomatic, but symptomatic patients commonly show chest pain, cough, or hemoptysis. A peripheral coin lesion in the lung is the typical characteristic of human dirofilariasis, but this pulmonary nodule may simulate primary or metastatic lung tumor. One infection of a Thai patient with *D. immitis* was presented by a cyst in the lung; a series of cystic sections showed particular characteristics of a dog's heartworm. This study aimed to sero-differentiate one human dirofilariasis from other infections using female and male crude antigens. Serum antibodies were derived from nematodiases, cestodiases, trematodiases, protozoan infections, and healthy controls. The antibody of this patient reacted with 24.5 kDa female crude antigen, which does not react with antibodies of other serum samples and healthy controls. This antigen reacted with antibody against one Myanmar patient infected with *Wuchereria bancrofti* microfilariae. The antigens of male crude extract reacted with antibody of this case at 32 and 29 kDa, of which only 32 kDa reacted weakly with antibodies to some cases of cystic echinococcosis, sparganosis, paragonimiasis heterotremus, and minute intestinal fluke. The 29 kDa male crude extract was of interest for its diagnostic bands, but only one healthy control from Australia cross-reacted with this antigen. Serum antibody of this case showed negative to ICT (immunochromatographic tests to detect Bancroftian filariasis) and high titers with individual female and male crude antigens of *D. immitis* at 1:6,400 by IgG-ELISA. This research found two interesting antigens, 24.5 kDa female worm extract, and 29 kDa male worm extract, as differential diagnoses. Further study should conclude many cases of human dirofilariasis, and immunoblot testing should be further refined for greater specificity the 24.5 and 29 kDa bands for human dirofilariasis, and/or to produce ELISA-screening tests using a combination of both antigens with many lung infections and other diseases.

**Presented at:** Joint International Tropical Medicine Meeting, 29 November-1 December 2004, Ambassador Hotel, Thailand.

# SERODIAGNOSIS OF SUSPECTED ECHINOCOCCOSIS CASES USING NATIVE, PARTIALLY-PURIFIED, AND RECOMBINANT ANTIGENS

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**ECHINOCOCCOSIS** is a rare disease in Thailand. All suspected cases were either serodiagnosed or parasitologically tested for the infection. Indirect ELISA has been used to screen for negative results at the Department of Helminthology, Faculty of Tropical Medicine, Mahidol University. Twenty-four serum samples were from non-Thai and Thai patients, and were collected from 1986 to 2003. All sera were tested to obtain positive results by indirect ELISA and immunoblot at the Department of Parasitology, Asahikawa Medical College, Hokkaido, Japan. Antigens from both *Echinococcus granulosus* and *E. multilocularis* were used, eg., cystic fluid (HCf/sheep, AgB), fractionated cystic fluid of alveolar cyst (Em22F9&11 Ag, AEc) and recombinant antigen (rAgB). Only one Thai patient had higher ODs-ELISA (0.922, 1.140 and 1.386) than

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Key words: cystic and alveolar cystic fluid antigens, IgG-ELISA, IgG-immunolot

**Presented at:** Joint International Tropical Medicine Meeting, 29 November-1 December 2004, Ambassador Hotel, Thailand

the positive controls (0.651, 1.121 and 1.358) against Em22F9&11 Ag, HCf/sheep (AgB) and recombinant antigens, respectively. Antibodies of the rest produced lower ODs against three antigens, but one Thai patient had OD (0.633) against Em22F9&11 Ag close to that of the positive control. A Thai patient, in whom protoscolecies were found, had far lower ODs (0.440, 0.377 and 0.063) than controls against Em22F9&11 Ag, HCf/sheep (AgB) and recombinant antigen, respectively. Ten serum samples of high ODs-ELISA, (both higher and lower ODs than the positive controls), were tested specifically for antibodies against AgB of HCf/sheep by immunoblot. There were four suspected cases, two non-Thai and two Thai patients, and the protoscolex-positive case presented immunoblot-positive using this AgB. The investigation of echinococcosis detection is more successful in use of immunoblot than indirect ELISA.

# ECHINOCOCCOSIS INCIDENCE IN THAILAND

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Key words: echinococcosis incidence, native cystic fluid antigen, IgG-ELISA,

**Presented at:** Joint International Tropical Medicine Meeting, 29 November-1 December 2004, Ambassador Hotel, Thailand.

**ALTHOUGH** echinococcoses are rare diseases in Thailand, the incidence of both cystic and alveolar echinococcoses is increasing. Eighteen indigenous and imported echinococcoses cases with protoscolex findings have been reviewed since 1936. In 2004, another alveolar echinococcosis case of a Thai patient was found but it has not yet been reported in the literature. Our laboratory received forty-seven suspected or presumptive serum and cystic fluid samples of echinococcosis, which were mostly sent from other hospitals. The patients were Thai residents and a number of patients were from the Middle East. The specimens were examined by parasitological or immunological techniques. Cystic echinococcosis cases, two protoscolex-proven cases were included in the review and another five cases have not been reported by the concerned physicians. Many cases presented clinical manifestations at the affected organs with a cyst. In only one Thai case, a single cyst had been found some years, beforehand which was accidentally ruptured while playing football, protoscolices were found. Due to limited antigen, cross-reactivity was not able to be tested with a high number of serum samples from different diseases. Our serodiagnostic service reports only negative results of indirect ELISA to rule out cystic echinococcosis. The majority of serum samples gave negative results with low ODs-ELISA close to the ODs of the negative controls and far lower than those of the positive controls. Only five cases gave ODs-ELISA higher the positive controls. Recently, we obtained cystic fluid antigen from a human case, and we will perform immunoblot for sensitivity and specificity of tests of with this antigen. From the literature review, unreported cases and our data collection from patients, most echinococcus cysts were found in the liver and the lung, while they were also found in the abdomen, kidney, jaw and foot. The incidence of cystic and alveolar echinococcoses in Thailand is increasing by 1) imported Thai cases who have worked in the Middle Eastern countries, 2) patients from the Middle Eastern countries both referred to and requiring operations at hospitals in Bangkok, 3) indigenous cases, probably infected with *Echinococcus* egg by any means of transmission.

# DETECTION OF IGG ANTIBODIES OF BRUGIAN FILARIASIS WITH CRUDE MALE AND FEMALE ANTIGENS OF *DIROFILARIA IMMITIS*

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*Key words:* Dirofilaria immitis *male and female crude antigen, Brugian filariasis, IgG-ELISA*

**CRUDE** antigens from male and female *Dirofilaria immitis* were applied to detect antibody to Brugian filariasis in humans by indirect ELISA. Both antigens were tested with 42 cases of Brugian filariasis, 131 cases of 20 heterologous infections and 35 healthy controls. The results, using male and female antigens, showed sensitivity of 88.1% and 88.1%, and specificity of 64.1% and 51.8%, respectively. Cross-reaction from other helminthic infections using crude male antigen gave false-positive with 48 sera from 13 heterologous diseases at the threshold value, 0.180, while the female antigen gave 63 sera from 15 diseases, at 0.309. Serum antibodies from patients with other helminthic infections-gnathostomiasis, strongyloidiasis, hookworm infections, trichinellosis, capillariasis, angiostrongyliasis, ascariasis, trichuriasis, toxocariasis, neurocysticercosis, cystic echinococcosis, taeniasis, opisthorchiasis-resulted in false-positive with both male and female antigens. One each of sparganosis and paragonimiasis heterotremus sera cross-reacted with only crude female antigen and their OD values were close to the threshold value. Although crude male antigen showed better specificity results than crude female antigen, both female and male worms are a source of antigens needed for further purifications. This study provides baseline data for further serodiagnosis of Brugian filariasis using dirofilaria antigen.

**Presented at:** Joint International Tropical Medicine Meeting, 29 November-1 December 2004, Ambassador Hotel, Thailand

# MULTI-IMMUNODOT FOR RAPID DIFFERENTIAL DIAGNOSIS OF EOSINOPHILIC MENINGITIS DUE TO PARASITIC INFECTIONS

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**A** multi-dot ELISA was developed for the rapid and simple differential diagnosis of eosinophilic meningitis due to helminth infections. Ultrafiltrated, purified antigens of *Parastrongylus* (= *Angiostrongylus*) *cantonensis*, *Gnathostoma spinigerum* and *Taenia solium* metacestodes, the most common parasites that invade the central nervous system and cause peripheral eosinophilia, were dotted onto a single nitrocellulose membrane strip. The antigen-coated strips, when blocked with 5% skimmed milk and dried, were stable for at least 6 months at 4 C. with peroxidase conjugated anti-human immunoglobulins and 4-chloro-1-naphthol as a substrate, antibodies in the corresponding patient sera were clearly detected on the membrane strip as well defined blue dots. Although cross-reactions between *P. cantonensis* and *G. spinigerum* antigens were observed with the use of partially purified antigens, the darkest dot correlated well with the infecting parasites in all cases. This fast, easy and economical multiple dot-blot ELISA method is useful for the differential diagnosis of eosinophilic meningitis caused by parasitic helminthes as semi-purified antigens can be easily obtained by untrafiltration and used. Further improvement using highly specific parasite antigens may make this multi-immunodot test more suitable for wide-scale use in studies and diagnostic laboratory.

**Presented at:** Joint International Tropical Medicine Meeting, 29 November-1 December 2004, Ambassador Hotel, Thailand

# HOST-FINDING BEHAVIOR OF *STRONGYLOIDES STERCORALIS* INFECTIVE LARVAE TO SODIUM CATION, HUMAN SERUM AND SWEAT

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*Key words:* Strongyloides stercoralis *infective larvae, chemicals, sweat*

**THE** host-finding behavior of *Strongyloides stercoralis* infective larvae was examined by *in vitro* agarose assay method. First, as human body fluid contains 0.85% (*ca* 0.15 Molar) NaCl, various concentrations of sodium chloride from 0.5M to 0.01M (7 steps), were examined and many larvae were attracted at concentrations between 0.5 and 0.05M of sodium chloride. 0.05M attracted the most number of larvae. 0.02M of sodium chloride showed greatly reduced larval attraction than 0.05M. Therefore, the threshold concentration was determined as 0.05M. Then, 0.05M of chemicals were examined in a further experiment. Chloride compounds (NaCl, KCl, $CaCl_2$, $MgCl_2$) were investigated. These chemicals are components of human body fluids. Distilled water was used as control in all experiments. Sodium chloride only attracted the larvae. Next, alkaline compounds were examined, ie. NaOH, KOH, $Ca(OH)_2$ and $Mg(OH)_2$. Larvae accumulated only at the NaOH site. The results suggest that the Na cation is important for larval attraction. A high pH value did not influence attraction at all. Next, human serum was tested. The human serum used was from normal serum to 1/32 diluted sera by distilled water (7 steps). Hierarchical attraction was seen according to the serum concentrations. Next, human sweat was collected from a limited zone of chest skin where only eccrine glands were distributed. Non-diluted sweat attracted the most number of larvae. Sweat might act as one of the most probable factors for infection of this skin penetrating nematode.

**Presented at:** Joint International Tropical Medicine Meeting, 29 November-1 December 2004, Ambassador Hotel, Thailand

# MR IMAGING FINDING IN CEREBROSPINAL GNATHOSTOMIASIS

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**HUMAN** gnathostomiasis is an infection caused mainly by *Gnathostoma spinigerum*, a nematode. Infected humans can present with various clinical manifestations. Serology is the criterion standard for diagnosing gnathostomiasis, whereas MR imaging represents a complementary tool for assessing severity and extent of disease. We report two define cases of gnathostomiasis that were confirmed by the immunoblotting technique. MR imaging of the cervical cords showed cord enlargement and difuse high signal intensity, mainly of the gray-white matter regions. MR imaging of the brain showed hemorrhagic tract and scattered deep intracerebral hemorrhage with diffuse, fuzzy white matter lesions with nodular enhancement. Severe gnathostomiasis was unresponsive to treatment.

**Published in:** *AJNR Am J Neuroradiol* 2004;25:446-9.

# *GNATHOSTOMA* INFECTION IN FISH CAUGHT FOR LOCAL CONSUMPTION IN NAKHON NAYOK PROVINCE, THAILAND I. PREVALENCE AND FISH SPECIES

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**BETWEEN** August 2000 and August 2001, 12,216 fish of 73 species were purchased from several local markets in Nakhon Nayok Province, Thailand, and examined for the presence of *Gnathostoma* larvae. Almost all species were fresh-water fish that had grown naturally, rather than raised commercially. Eight species were

Keywords: Gnathostoma, fish, eel, Nakhon Nayok, Thailand

found to be infected with gnathostome larvae. The overall prevalence was 5.1% (626/12,216) and a total of 5,969 larvae was recovered. The highest rate of infection (30.1%) was found in *Monopterus albus* (swamp eel). The rates in the remaining infected fish were as follows: *Anabas testudineus* (climbing perch) 7.7%, *Channa striata* (striped snake-head fish) 7.4%, *Clarius macrocephalus* (Gunther's walking catfish) 6.7%, *Channa micropeltes* (giant snake-head fish) 5.1%, *Channa lucius* (blotched snake-head fish) 4.0%, *Clarius batrachus* (Batrachian walking catfish) 1.4%, and *Ompok krattensis* (butter sheatfish) 0.6%. The mean number of larvae/fish was highest in swamp eels (10.0 larvae/eel), and the maximum number of 698 larvae was recovered from one eel. The body sizes of the recovered *G. spinigerum* advanced third-stage larvae were 2.70-5.10 mm in length (average, 3.97 ± 0.50 mm) and 0.29-0.60 mm in width (average, 0.40 ± 0.04 mm). The average number of cephalic hooklets of the larvae from rows 1 to 4 were 41.8 ± 0.5 (range, 40-43), 43.6 ± 0.6 (range, 42-45), 46.1 ± 0.9 (range, 44-48) and 49.3 ± 0.7 (range, 48-51), respectively.

**Published in:** *Southeast Asian J Trop Med Public Health* 2004;35:523-30.

# *GNATHOSTOMA* INFECTION IN FISH CAUGHT FOR LOCAL CONSUMPTION IN NAKHON NAYOK PROVINCE, THAILAND II. SEASONAL VARIATION IN SWAMP EELS

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*Keywords:* Gnathostoma, *swamp eels, Nakhon Nayok, Thailand*

**FROM** August 2000 to August 2001, 1,844 swamp eels (*Monopterus albus*) were purchased from several local markets in Nakhon Nayok Province, Thailand, and examined for the presence of *Gnathostoma* advanced third-stage larvae. The overall prevalence was 30.1% and the mean number of larvae/eel (infection intensity) was 10.0. The highest infection rate (44.1%) was found in August 2000 and the lowest (10.7%) in March 2001. The greatest mean number of larvae/eel (75.1) was found in August 2000, whereas the fewest (2.3) was in July 2001. It is suggested that the prevalence and intensity of infection decreased within two months after the end of the rainy season and started to rise again about two months after the next rainy season began. A total of 5,532 *Gnathostoma* larvae were recovered from 555 infected eels, with a maximum number of 698 larvae/eel. The highest rates of *Gnathostoma* infection according to eel body length and weight were 87.5% in the group 91-100 cm, and 100% in groups of 901-1,100 g, respectively. There were significant correlations between eel body lengths and infection rates, body lengths and infection intensities; eel body weights were also significantly correlated with infection rates and infection intensities. It was noted that the longer/heavier the eels were, the higher would be the infection rates and the greater the infection intensities.

Tissue distributions of *Gnathostoma* larvae in the livers and muscles of swamp eels were as follows: 43.0% of the total number of larvae were found in the muscles and 57.0% were in the liver; 29.7, 51.7 and 18.6% were in the anterior, middle, and posterior parts, respectively; 35.1% were in the dorsal part, while 64.9% were in the ventral part; 9.0, 18.7, 7.4, 20.6, 33.1, and 11.2% were in the anterodorsal, mediodorsal, posterodorsal, anteroventral, medioventral and posteroventral parts, respectively. Of the 5,532 *Gnathostoma* larvae examined, 1,101 (19.9%) were found to possess morphological variants or abnormal cephalic hooklets. The most common unusual feature was that there were few to numerous extra rudimentary hooklets below row 4 and between the 4 rows of hooklets (7.6%), the presence of a fifth row of hooklets (3.5%), abnormal hooklets in any of the 4 rows of hooklets (5.2%), spiral arrangement of the 4 rows of hooklets (1.8%), and larvae having only 3 rows of hooklets (0.3%).

**Published in:** *Southeast Asian J Trop Med Public Health* 2004;35:x-y.

# SOIL-TRANSMITTED HELMINTHIASES AND HEALTH BEHAVIORS AMONG SCHOOLCHILDREN AND COMMUNITY MEMBERS IN A WEST-CENTRAL BORDER AREA OF THAILAND

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**THE** prevalence of soil-transmitted helminthic infections and health behaviors related to infections in schoolchildren and villagers of a community (4 hamlets) was studied in Hauy Kayeng subdistrict, Thong Pha Phum district, in the north of Kanchanaburi Province. The intestinal helminth infection rate of the schoolchildren was 15.6%. Hookworm infection was the most prominent (9.8%), followed by *Trichuris trichiura* (6.2%), and *Ascaris lumbricoides* (2.2%). The community showed higher prevalence rates and was infected with more types of intestinal helminths than the schoolchildren. Thirty-five point two percent (35.2%) of the residents were infected with soil-transmitted helminths, 30.5% with hookworm, 3.4% with *A. lumbricoides* and 2.2% with *T. trichiura*. Almost all hookworm cases (94.3%) were light intensity infections, while only 1.3% were heavy infections. Moreover, the hookworm infection rate in the community was found to be much higher when a stool culture method was used (39.1%). With this technique, 2.3% *Strongyloides stercoralis* infections were detected in the community population. Examination of the health behavior of the study samples showed that approximately 75% always defecated in a toilet. Schoolchildren who always wore shoes comprised 67%, which was lower than the community, at 85%.

**Published in:** *Southeast Asian J Trop Med Pulbic Health* 2004; 35: 260-6.

# WATERBORNE ZOONOTIC HELMINTHIASES

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*Keywords: Snails; Copepods; Faecal contamination; Schistosomiasis; Cercarial dermatitis; Swimmer's itch; Fascioliasis; Fasciolopsiasis; Sparganosis; Gnathostomiasis; Dracunculiasis; Cysticercosis; Hydatid disease; Larva migrans*

**THIS** review deals with waterborne zoonotic helminths, many of which are opportunistic parasites spreading directly from animals to man or man to animals through water that is either ingested or that contains forms capable of skin penetration. Disease severity ranges from being rapidly fatal to low-grade chronic infections that may be asymptomatic for many years. The most significant zoonotic waterborne helminthic diseases are either snail-mediated, copepod-mediated or transmitted by faecal-contaminated water. Snail-mediated helminthiases described here are caused by digenetic trematodes that undergo complex life cycles involving various species of aquatic snails. These diseases include schistosomiasis, cercarial dermatitis, fascioliasis and fasciolopsiasis. The primary copepod-mediated helminthiasses are sparganosis, gnathostomiasis and dracunculiasis, and the major faecal-contaminated water helminthiases are cysticercosis, hydatid disease and larva migrans. Generally, only parasites whose infective stages can be transmitted directly by water are discussed in this article. Although many do not require a water environment in which to complete their life cycle, their infective stages can certainly be distributed and acquired directly through water. Transmission via the external environment is necessary for many helminth parasites, with water and faecal contamination being important considerations. Human behaviour, particularly poor hygiene, is a major factor in the re-emergence, and spread of parasitic infections. Also important in assessing the risk of infection by water transmission are human habits and population density, the prevalence of infection in them and in alternate animal hosts, methods of treating sewage and drinking water, and climate. Disease prevention methods, including disease surveillance, education and improved drinking water treatment are described.

**Published in:** *Vet Parasitol* 2004;126: 167-93.

# INTESTINAL PARASITIC INFECTIONS AMONG INHABITANTS OF THE NORTH, WEST-CENTRAL AND EASTERN BORDER AREAS OF THAILAND

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**AFTER** the 8th Health Development Plan in the year 2001, the Ministry of Public health, Thailand, reported that the prevalence rate of liver fluke infection was 9.6%, and hookworm infection 11.4%. The data were collected from 30 sample clusters in each of 12 public health regions, but remote areas along the border were excluded. Mountainous areas in tropical zones are favorable for the transmission of parasitic diseases; populations inhabitating the mountains along border areas may harbor several kinds of parasties. Since population migration in these areas in common, disease transmission form place to place is possible and may affect the Intestinal Helminthiasis Control Prugram of the country. In this study, the prevalence of intestinal parasites among populations located along the borders between Thailand-Laos (Nan Province); Thailand-Myanmar (Kanhanaburi Province) and Thailand-Cambodia (Sakaeo Province) were investigatd. Stool examinations by Kato-Katz method revealed that the prevalence rates of helminthic infection of 55.8% in Nan, 49.4% in Kanchanaburi, and 49.5% in Sakaeo.

The species of helminths found in these areas were *Necator americanus, Ascaris lumbricoides, Trichuris trichiura, Strongyloides stercoralis, Enterobius vermicularis, Hymenolepis nana, Opisthorchis viverrini, Haplorchis taichui, Taenia saginata, T. solium, and Paragonimus* sp. The hookworm infection rates in Nan and Kanchanaburi were 25.5% and 46.2%, respectively. In Nan province, 15.4% of the hookworm cases were in heavy and moderate, while 49.7% of ascariasis cases were classified as heavy and moderate. In Sakaeo, most of the infected population harbored liver fluke (47.9%). It was proved that in the northern border area (Nan Province), the small trematode eggs found in stool samples belonged to the minute intestinal fluke, *Haplorchis taichui*. One case of paragonimiasis was found in a girl from Nan Province. Many cases of taeniasis were also detected by stool examination.

Intestinal protozoa rates among the populations in Nan, Kanchanaburi, and Sakaeo were 30.8, 47.7 and 38.5%, respectively. Infections of *Blastocystis hominis, Entamoeba coli, Giardia intestinalis,* and *Entamoeba histolytica* were common among villagers near the borders, and some rare species of protozoa were observed among them, such as *Cyclospora cayetanensis, Chilomastix mesnili* and *Sarcocystis hominis.*

**Published in:** *J Trop Med Parasitol* 2004; 27: (2)

# HELMINTH INFECTIONS IN PRACHUAP KHIRI KHAN, CHUMPHON AND KHON KAEN PROVINCES

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***Keywords:*** *Prevalence, helminth, Prachuap Khiri Khan, Chumphon, Khon Kaen, Thailand*

**THE** prevalence of intestinal helminth infections was sstudies in ten primary schools in Bang Saphan District, Prachuap Khiri Khan Province, in four primary schools in Lang Suan District, Chumphon Province, and in rural populations in Muang, Phrayun and Ubonrat districts, Khon Kaen Province, using Katz's modified thick smear technique. In Prachuap Khiri Khan Province, a total of 826 fecal samples was collected in July 2003. It was found that 8.0%(66/826) were infected: 7.0% with hookworm, 0.1% with *Ascaris lunbricoides*, 0.6% wirh *Trichuris trichiura*, 0.4% with *Enterobius vermicularis*, and 0.2% wirh *Humenolepis nana*. In Chumpon Province, 436 fecal samples were collected in July 2003. The overall infection rate was 9.9%(43/436): 7.1% with hookworm, 0.7% with

*A. lumbricoides*, and 2.8% with T. trichiura. In Khon Kaen Province, 1,222 fecal sample were collected in November 2003; 10.5%(128/1,222) were infected, 1.9% with hookworm, 0.2% with *T. trichiura*, 0.2% with *Strongyloides stercoralis*, 0.8% with *Taenia* sp, 7.1% with *Opisthorchis viverrini*, and 0.6% with *Echinostoma* sp. All positive samples revealed low infection intensity, except for only four hookworm cases, two each from Prachuap Khiri Khan and Chumphon provinces, having moderate infection intensity.

**Published in:** *J Trop Med Parasitol* 2004;27:11-4.

## CHEMOTACTIC ATTRACTION OF *NECATOR* HOOKWORM FILARIFORM LARVAE TO SODIUM CHLORIDE

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**AN** investigation was carried out to elucidate the chemotactic attractive behavior of *Necator* hookworm filariform larvae to inorganic substances *in vitro*. First, an optimal concentration of these larvae against sodium chloride solutions using the agarose plate assay method was determined. The sodium chloride concentration varied from 0.1 to 1.0 molar solutions. Distilled water (DW) was used as control in all experiments. 0.5 molar was found to be an appropriate concentration to examine larval attraction. Then, chloride compounds such as NaCl, KCl, $CaCl_2$ and $MgCl_2$ were tried at 0.5 molar concentration; many larvae were attracted to NaCl and some also to KCl. Therefore, the same experiment was conducted using 0.1 molar chemical concentrations. Many larvae were attracted to NaCl; however, some larvae again moved to KCl. Next, the concentration was changed to a higher range, 1.0 molar, and as a result, NaCl only attracted the larvae. The larvae were not attracted to 1.0 molar of KCL, $CaCl_2$, and $MgCl_2$. Since the chloride anion was found not to attract larvae of this species, another experiment was conducted with 0.5 molar of the sodium compounds, $Na_2Co_3$, NaOH, $NaHCO_3$, NaCl, and DW. $Na_2CO_3$, had the strongest larval attracting ability. Other sodium compounds also attracted moderate numbers of larvae. In the inorganic substances tried, the sodium cation was found to attract *Necator* larvae, and thus the sodium cation might have an important role for finding and infecting hosts of *Necator* hookworm filariform larvae.

**Published in:** *Southeast Asian J Trop Med Public Health* 2004;35: 112-5.

## IDENTIFICATION OF *BRUGIA MALAYI*-LIKE MICROFILARIAE IN NATURALLY-INFECTED CATS FORM NARATHIWAT PROVINCE, SOUTHERN THAILAND

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*Keywords : cats,* Brugia malayi-*like microfilariae, morphometry*

**BRUGIA MALAYI-LIKE** microfilariae from 21 naturally infected cats were identified by microfilarial morphometry and acid phosphatase activity. The results revealed that the average innenkorper length of 28.56 ± 6.08 mm and intensely positive sites of acid phosphatase activity at the amphids, excretory vesicles, anal vesicles and phasmids were compatible with *B. malayi* microfilariae, thus emphasizing the important role of cats as a reservoir host of *B. malayi* in Narathiwat Province, southern Thailand.

**Published in:** *J Trop Med Parasitol* 2004;27:21-5.

# ZYMOGRAM PATTERNS OF *NAEGLERIA* SPP ISOLATED FROM NATURAL WATER SOURCES ON TALING CHAN DISTRICT, BANGKOK

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*Key words : Naegleria spp., zymogram*

**A** genetic approach was cited for species detection of the ameba genus *Naegleria* using allozyme electrophoresis to characterize the trophozoite stage of three strains of *Naegleria fowleri* isolated from patients with primary amebic meningoencephalitis, five thermophilic (45°C) *Naegleria* spp isolated from natural water sources in the Taling Chan district, and a reference control strain, *Naegleria fowleri* CDC VO 3081. Isoenzymes of ameba whole-cell extracts were analyzed by vertical polyacrylamide slab gel electrophoresis to determine whether there was any correlation between different strains of the ameba. The results showed that five out of fifteen enzymes; aldehyde oxidase (ALDOX), aldolase (ALD), α-glycerophosphate dehydrogenase (α-GPDH), xanthine dehydrogenase (XDH), and glutamate oxaloacetate transaminase (GOT), were undetectable in the pathogenic strains, while the other enzymes; esterase (EST), fumerase (FUM), glucose-6-phosphate dehydrogenase (G-6-PDH), glucose phosphate isomerase (GPI), isocitate dehydrogenase (IDH), lactate dehydrogenase (LDH), leucine aminopeptidase (LAP), malic enzyme (ME), glucose phosphomutase (GPM), and malate dehydrogenase (MDH), were detectd. *Naegleria fowleri* strains were biochemically the most homogeneous. They showed intraspecific isoenzyme variation that allowed them to be grouped. In contrast, the allozyme patterns (EST 1-7, IDH) of *Naegleria* spp isolated from the environment showed interspecific isoenzyme variations from the pathogenic *Naegleria* strain. In conclusion, this study recognized the zymograms of the *Naegleria fowleri* strains were heterogenically different from the thermophilic 45°C *Naegleria* spp isolated from the environment.

**Published in:** *Southeast Asian J Trop Med Public Health* 2004;35(2):275-80.

# LABORATORY AND FIELD TRIAL OF DEVELOPING MEDICINAL LOCAL THAI PLANT PRODUCTS AGAINST FOUR SPECIES OF MOSQUITO VECTORS

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*Key words:* Syzygium aromaticum, Zanthoxylum limonella, *Mosquito repellents*

**OILS** of *Syzygium aromaticum* (clove), *Zanthoxylum limonella* (makaen), widely used essential oils for dental caries or flavoring of food in Thailand, were prepared as 10 experimental repellent products in gel or cream forms against *Aedes aegypti*, *Culex quinquefasciatus*, and *Anopheles dirus* under laboratory conditions, using the human-arm-in-cage method. Two products that gave the longest-lasting complete protection were selected to examine their repellency against a variety of mosquito species under field conditions. In laboratory tests, 0.1 g of each product was applied to 3x10 cm of exposed area on a volunteer's forearm, while in field trials, 1.0 g was applied to each volunteer's leg (from knee to ankle). In the laboratory, the gel dosage form contained 20% clove oil (Gel B) or 10% clove plus 10% makaen oil mixture (Gel E) were promising plant-based repellents against three mosquito species and gave significantly longer complete protection times of 4-5 hours than all other developing products. Therefore, their efficacy in the field was evaluated. Under field conditions, Gel E showed complete protection for 4 hours and gave 95% repellency after 5 hours application, whereas Gel B and 20% deet (di-methyl benzamide) provided only 86.8 and 82.7% repellency after treatment, respectively against *Ae. aegypti*, daytime-biting mosquitos. For nighttime-biting, the 3 repellents under development yielded equally excellent (average 97.1%) repellency for 5 hours against the predominant *Cx. quinquefasciatus* and *Mansonia uniformis*, but they gave 89.0% repellency against *Cx. tritaeniorhynchus* and *Cx. gelidus*. This finding demonstrated the effectiveness of Gel B and Gel E products for possible use by low-income rural communities against various mosquito species.

**Published in:** *Southeast Asian J Trop Med Public Health* 2004;35(2):325-33.

(Supported by The Thailand Research Fund (TRF) from a grant of the Royal Golden Jubilee (RGJ) Ph.D. program)

# MARKEDLY REDUCED SEVERITY OF DENGUE VIRUS INFECTION IN MOSQUITO CELL CULTURES PERSISTENTLY INFECTED WITH *AEDES ALBOPICTUS* DENSOVIRUS (*AAL*DNV)

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*Key words : Densovirus, Dengue virus, Persistent infection*

**AALDNV-INFECTED** C6/36 cells serially passaged for over 10 weeks showed a decline in percentage of anti-*Aal*DNV-positive cells (APC) from an initial 92% to approximately 20%. Cultures of persistent APC were indistinguishable from uninfected cultures by direct microscopy but most stained cells from early APC passages had enlarged nuclei with eosinophilic inclusions, while late APC passages had few and naive cells none. Super challenge of persistent APC cultures did not increase percentage APC and supernatants from persistent APC cultures gave low APC (40%) in naive C6/36 cell cultures. When challenged with dengue virus serotype 2 (DEN-2), naive C6/36 cells showed severe cytopathic effect (CPE) and high mortality within 4 days, as did early passage APC cultures. Remarkably, DEN-2 infections in persistent APC cultures were much less severe, being characterized by reduced DEN-2 infection percentage, retarded DEN-2 virion production, no CPE and no significant mortality. Reasons for rapid reduction in APC and resistance to superinfection upon serial passage remain unproven but may relate to production of *Aal*DNV-defective interfering particles (DIP) by molecular mechanisms still open to speculation. More difficult to explain is cross-protection against DEN-2 induced mortality seen in persistent APC cultures. However, by comparison to work on shrimp viruses, we speculate that this may involve blockage of viral-triggered apoptosis. The phenomena described raise questions regarding the potential for persistent infections by unknown viruses to confound experimental results with insect cell lines.

**Published in**: *Virology* 2004;329:261-9

(Supported by the National Center for Genetic Engineering and Biotechnology (BIOTEC), National Science and Technology Development Agency (NSTDA), Thailand)

# BIONOMICS STUDIES OF *MANSONIA* MOSQUITOES INHABITING THE PEAT SWAMP FOREST, "PHRU TOH DAENG", NARATHIWAT PROVINCE

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*Key words : Bionomics,* Mansonia *mosquito, peat swamp forest*

**THE** present study was conducted during 2000-2002 to determine the bionomics of *Mansonia* mosquitoes, vectors of nocturnally subperiodic *Brugia malayi*, inhibiting the peat swamp forest, "Phru Toh Daeng", Narathiwat Province. 54 species of mosquitoes belonging to 12 genera were added for the first time to the list of animal fauna in the peat swamp forest. *Mansonia* mosquitoes were most abundant (60-70%) by all collection means and occurred throughout the year with high biting density (10.5-57.8 bites per person-hour). *Ma. bonneae* was most prevalent (47.5%) and fed on a variety of animal hosts including domestic cats, cows, monkeys and heavily on man with maximum biting density during our study period of 24.3 bite per person-hour in October. The infective bites were found in *Ma. annulata* (1300-1400 hours) for the first time collected at Ban Toh Daeng and also *Ma. bonneae* at forest shaded (1600-1700 hours) and the village (2000-2100 hours) with rates of 0.6, 1.1. and 1.0%, respectively. Biting activities of these two species occurred during day and night time with 2 lower peaks at 1000 hours (18.5 bites per person-hour) and between 1300-1500 (8.5-10.0 bites per person-hour) hours and the highest peak between 1900-2100 hours (31.5-33.0 bites per person-hour), respectively. The biting

activity patterns were correspondent with the periodicity found in man and domestic cats and might play an important role in either transmission or maintenance of the filarial parasites in the peat swamp forest. The relative role of *Ma. bonneae* and *Ma. uniformis* in different environmental settings (primary swamp forest and open swamp) on the transmission of nocturnally subperiodic *B. malayi* merits further study.

**Oral presentations in:** Joint International Tropical Medicine Meeting 2004, Ambassador Hotel, Bangkok, Thailand, 29 November-1 December 2004.

## SURVEYS FOR NATURAL HOST PLANTS OF *MANSONIA* MOSQUITOES INHABITING "TOH DAENG" PEAT SWAMP FOREST, NARATHIWAT PROVINCE

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*Key words :* Host plants, Mansonia mosquitoes, peat swamp forest

THE surveys were carried out monthly during April to Octorber, 2002 and examined 68 sampling sites around "Toh Daeng" peat swamp forest, Narathiwat Province of which 38 were known *Mansonia*-positive habitats and 30 were *Mansonia*-negative sites. The present larval surveys were just qualitative one owing to host plants characteristics (location, distribution and abundance), difficulties in locating and selecting the host plants in the swamp forest and time constraints. The attempts to search for host plants were more than 20 times for each plant species until the larvae were found. The confirmation of the presence of *Mansonia* larvae on each plant species was 6 times on different plants and locations. The larvae of *Ma. bonneae* and *Ma. uniformis* were obtained form eighteen plant species (10 families) namely *Metroxylon sagu*, *Melaleuca cajuputi*, *Pandanus militaris*, *Pandanus immerses*, *Hanguana malayana*, *Typha angustifolia*, *Hymenachne acutigluma*, *Scirpodendron ghaeri*, *Scleria sumatrensis*, *Rhynchospora corymnosa*, *Sacclolepis indica*, *Cyperus babakan*, *Chyperus corymbosus*, *Lepironia articulata*, *Leersia hexandra*, *Eichornia crassipes*, *Pistia stratriotes* and ferns. The aquatic plants – *S. ghaeri*, *S. sumatrensis*, *H. acutigluma*, *R. corymnosa*, *S. indica*, *C. babakan*, *C. corymbosus*, *L. articulata* were the common host plants. Samples from larger trees, *M. sagu* and *M. cajuputi* yielded only low number (1-7) larvae per scraping. *Ma. uniformis* was recovered from most of the host plants, however, *Ma. bonneae* preferred submerged plants and was not collected from floating aquatic plants, *E. crassipes* and *P. stratriotes*. The description of modified dipper and dipping technique were given and discussed.

**Poster presentations in:** Joint International Tropical Medicine Meeting 2004, Ambassador Hotel, Bangkok, Thailand, 29 November-1 December 2004.

## LABORATORY COLONIZATION OF *MANSONIA* MOSQUITOES WITH AN EMPHASIS ON *MA. ANNULATA* AND *MA. BONNEAE*

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*Key words :* Mansonia, Lepironia articulata, *lizard droppings*

THE present study records the first successful colonization of *Ma. annulata* and describes colony maintenance with modification of rearing medium and host plants. Three species of *Mansonia* mosquitoes (*Ma. uniformis*, *Ma. indiana* and *Ma. annulifiera*) were successfully reared at the ambient environments with the adult emergence rates over 50%, while *Ma. bonneae* and *Ma. dives* yielded emergence rates of over 30%. Colonization of *Ma. annulata* was modified and improved so that it could be reared until the adult emergence. Tube sedge, *Lepironia articulata* was utilized as the host plant and peat swamp water was used as rearing medium. Yeast and lizard droppings were added daily to the larval medium to maintained microorganisms and pH in the infusion. *Ma. annulata* was then successfully raised to the adults with emergence rates of 23%. However, identifying suitable culture medium remains an obstacle to establishing colonies of *Ma. annulata* as the culture medium is difficult to mimic in the laboratory. Further study focussing particularly on larval attachment substrates and the rearing medium is needed to develop a more standardized and practical rearing tecnique for *Mansonia* mosquitoes.

**Poster presentations in:** Joint International Tropical Medicine Meeting 2004, Ambassador Hotel, Bangkok, Thailand, 29 November-1 December 2004.

# THE RELATIONSHIP BETWEEN THE ABUNDANCE OF *MANSONIA* MOSQUITOES INHABITING PEAT SWAMP FOREST AND REMOTELY SENSED DATA, NORMALIZED DIFFERENCE VEGETATION INDEX (NDVI) AND LAND SURFACE TEMPERATURE (LST)

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*Key words : Nomalized Difference Vegetation Index (NDVI), Land Surface Temperature (LST),* Manosnia *mosquitoes*

**THE** role environmental determinants such as elevation, temperature, rainfall, and humidity influencing the presence, development, activity, and longevity of pathogens, vectors, zoonotic reservoirs of infection, and the epidemiology of vector-borne diseases is well known. Previously works suggested that it might be possible to predict adult abundance in advance using data on the vegetation index (NDVI), rainfall and temperature. The present study was to demonstrate relationship of some environmental factors, vegetation greenness index (NDVI) and land surface temperature (LST) with the seasonal variations of *Mansonia* mosquitoes (*Ma. bonneae* and *Ma. uniformis*) in Khosit subdistrict, Narathiwat Province. *Mansonia* pupulation lagged by one month responded positively to NDVI, LST and rainfall what means that a rise in the number of the mosquitoes was directly related to the rise in vegetation, temperature and rainfall. The present study did not attempt to draw a definitive picture of seasonal abundance of *Mansonia* mosquitoes in relation to these environmental variables. The direct causal link between these environmental factors and the mosquito density in the peat swamp forest is of research interest. The measurements in higher frequency, more time series of field investigations and remotely sensed data would be needed to confirm their associations, to resolve the true response and study how the mosquitoes respond to the environmental factors.

**Poster presentationss in:** Joint International Tropical Medicine Meeting 2004, Ambassador Hotel, Bangkok, Thailand, 29 November-1 December 2004.

# SCREENING OF SOME THAI PLANT EXTRACTS FOR MOSQUITO LARVICIDE AND APPLICATION OF THE PROMISING RESULTS TO DOSAGE FORMS OF TABLET

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*Key words :* Rhinacanthus nasutus, *plant extracts, mosquito larvicide*

**FROM** the screening of 84 plants for mosquito larvicide activity, only six promising activities of ethanolic extracts from *Rhinacanthus nasutus, Derris elliptica, Trigonostemon redioides, Homalomena aromatica, Stemona tuberosa* and *Acorus calamus* were found to possess high potential larvicidal property with the 48 hour $LC_{50}$ values of 17.1, 26.9, 48.5, 50.6, 55.4 and 59.6 ppm, respecitively. The most promising 6 plants were selected for further investigation. From individual plant sample, two solvent extracts were obtained form the dried plant material by soxhlet extraction for 6 hr over a mantle heater at 60 C with petroleum ether (PE) and methanol (MeOH), respectively. Among the plant extracts studied, the larvicidal activity of both petroleum ether and methanol extracts of *R. nasutus* and *D. elliptica* were excellent. The PE extract of *R. nasutus* exhibited larvicidal effect against *Ae. aegypti, Cx. quinquefasciatus, An. dirus* and *Ma. uniformis* with $LC_{50}$ of 3.0, 14.5, 10.6 and 14.4 ppm, respectively while the MeOH extract presented $LC_{50}$ of 9.0, 11.2, 18.3 and 18.5 ppm, respectively. Likewise, *D. elliptica* of PE extract showed $LC_{50}$ of 13.3, 6.2, 7.3 and 23.7 ppm, respectively, but MeOH extract exhibited lower activity with $LC_{50}$ of 15.5, 24.8, 23.1 and 32.4 ppm, respectively. Activity of the PE and MeOH extract of *R. nasutus* were similarly most toxic against all four-mosquito species with $LC_{50}$ less than 19.0 ppm. Based on the above results and water solubility of the MeOH extract, *R. nasutus* was selected for developing as mosquito-larvicidal formulation at concentration of 5% and 10% table formulation. At dose that killed the mosquito larvae showed no harmful effect to the guppy fish (non-target organism). It is doubtless the *R. nasutus* provides some type of new compound for vector control, which is friendly to the environment.

**Oral presentation in:** 1st Asian Congress of Parasitology and Tropical Medicine and 40th Annual Scientific Seminar of Malasian Society of Parasitology and Tropical Medicine (MSPTM), Kuala Lumpur, Malasia, 23-25 March 2004.

(Supported by The Thailand Research Fund (TRF) from a grant of the Royal Golden Jubilee (RGJ) Ph.D. program)

# LABORATORY EVALUATION OF LOCAL PLANTS AS REPELLENTS AGAINST MOSQUITO BITE IN CAMBODIA

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*Key words : Cambodian plants, mosquito repellents, arm in cage test*

**Oral presentations in:** Joint International Tropical Medicine Meeting 2004, Ambassador Hotel, Bangkok, Thailand, 29 November-1 December 2004.

(Supported by The Commission on Higher Education (CHE), Thailand from a grant of the faculty and student exchange program between Thailand and neighbouring countries in the Greater Mekong Sub-region (GMS))

**ELEVEN** essential oils were extracted from Cambodian plants which have aromatic smell by using steam distillation equipment and were evaluated their repellent activity against uninfected laboratory strains of *Ae. aegypti* by using human arm-in-cage test. The results showed that Pros provided longest repellent effect and provided 3 hours 28 minutes of 100% protection. Jee bong tear gorn and Kbarl lmeat provided 2 hours protection time. Maras praou and Jee gerng protected for about 1 hr from mosquito bite. Thap tharo, Jee ong garm and Theum chhear were only slightly repellent to *Ae. aegypti*. Som bao krood and mixture oil of sesame and soybean were ineffective as mosquito repellents.

From a study of oil combinations, Formula E containing Pros, Jee bong tear gorn and Moras praou gave the longest protection of 4 hours 43 minutes while formula D containing Pros, Jee bong tear gorn, Kbarl lmeat, Pron lery and Moras praou provided the second best repellency of 3 hours 23 minutes. These oil-combinations gave more mosquito repellent activity than each pure oil which were their ingredients. These results indicated that the mixture of the effective oils provided synergistic activity especially Pros, Jee bong tear gorn and Moras praou.

# AN EVALUATION OF EXPERIMENTAL PLANT-BASED REPELLENTS AGAINST MOSQUITO BITES UNDER FIELD CONDITIONS IN THAILAND

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*Keywords:* Syzygium aromaticum, Zanthoxylum limonella, *Mosquito repellents*

**Poster presentation in:** XXII International Congress of Entomology, Brisbane, Queensland, Australia, 15-21 August 2004.

(Supported by The Thailand Research Fund (TRF) from a grant of the Royal Golden Jubilee (RGJ) Ph.D. program)

**TWO** experimental repellent products in the gel dosage form contained 20% clove oil (*Syzygium aromaticum*) alone and 10% clove oil in combination with 10% makaen (*Zanthoxylum limonella*) oil respectively, were evaluated for their efficacy against daytime- and nighttime-biting mosquitoes, comparing the two products with 20% deet (di-methyl benzamide) under field conditions using a human bait method. One gram of each product was applied evenly from knee to the ankle of each leg. Shorts and shoes were worn to standardize the exposure area. Other exposed untreated parts of the body were protected against mosquitoes attack by wearing a jacket with hood and gloves, covering the thighs with a plastic sheet. For daytime-biting, 20% clove showed complete protection for 4.0 h and demonstrated 95.7% repellency after 5 hrs application, whereas 10% clove plus 10% makaen oil mixture and 20% deet provided only 86.8 and 82.7% repellency after treatment, respectively against *Aedes aegypti*. For nighttime-biting, the 3 test repellents yielded equally excellent (average 97.1%) repellency for 5 hrs against the predominant *Culex quinquefasciatus* and *Mansonia uniformis* but they could only provide 89.0% repellency against *Cx. tritaeniorhynclus* and *Cx. gelidus*. These findings demonstrate that the repellency of 20% clove oil and 10% clove plus 10% makaen oil mixture in the gel dosage form are potential use against various different mosquito species.

# NOVEL MOSQUITO REPELLENTS DERIVED FROM ESSENTIAL OILS OF PLANTS IN THAILAND

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*Key words : repellent, essential oil, medicinal plants*

**MOSQUITO-BORNE** diseases, such as dengue, malaria and filariasis are serious public health problems in many countries, especially in the tropical regions of the world. These diseases are caused by pathogens that are transmitted to man through mosquito biting only, thus personal protection from mosquito bites is then considered as one of the strategies to prevent them. Efforts to develop alternatives to replace chemical repellents have been increasingly considered, including extracting and evaluating plant products for repellent activity. The development and use of locally available plant products showing repellent activity thus avails an alternative strategy for prevention of mosquito-borne diseases. In this study we evaluated and reported repellent effects of essential oils extracted from plants against 4 mosquito vectors: *Aedes aegypti*, *Ae. albopictus*, *Anopheles dirus* and *Culex quinquefasciatus* under laboratory conditions using human volunteers. The essential oils were extracted from various parts of 22 plant species, belonging to 10 families, and the oils were prepared as 10% solution in absolute ethanol and some additives. The essential oils showing high degree of repellency were subsequently formulated as topical repellents and tested against day- and night-biting mosquitoes under field conditions. The results obtained from both laboratory and field evaluations will be presented.

**Oral presentation in:** XII International Congress of Entomology, Brisbane, Queensland, Australia, 15-21 August 2004.

# THREE INDIGENOUS MEDICINAL THAI PLANTS FOR CONTROL OF *AEDES AEGYPTI* AND *CULEX QUINQUEFASCIATUS*

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*Key words : Larvicide, medicinal plant,* Aedes aegypti, Culex quinquefasciatus

**MOSQUITO-BORNE** diseases remain a major problem in the world, particularly in tropical and subtropical regions. The mosquitoes especially *Aedes* and *Culex* are known to be potential vectors for dengue hemorrhagic fever (DHF), yellow fever, Japanese encephalitis and lymphatic filariasis. The most available method for control of mosquito-borne diseases is the use of insecticides. However, there are many serious drawbacks with the use of chemical insecticides especially insecticide resistance and impact of environmental contamination. Thus the search for new safety compounds has been directed extensively at the plant kingdom. This study aimed to investigate the potential larvicidal activities and IGRs properties of crude ethanolic extracts of *Pueraria mirifica*, *Butea superba* and *Thevetia* peruviana against *Ae. aegypti* and Cx. *quinquefasciatus*. The bioassay of plant extracts against *Ae. aegypti* and *Cx. quinquefasciatus* on larvae were done according to World Health Organization guidelines (WHO, 1996). The late 3rd or early 4th instar larvae of *Ae. aegypti* and *Cx. quinquefasciatus* were tested with ethanolic extracts of selected three plants at a series of various concentrations. Mortality were recorded after 24 and 48 hours exposures for larvicidal activity and the continuous exposure were done and recorded for IGRs properties.

In case of larvicidal activiity, *T. peruviana* was the most potent followed by *P. mirifica* while *B. superba* was the least effective. In addition, the late 3rd instar was more susceptible than the early 4th instar larvae and the 48 hour exposure yielded more potent larvicide activity than 24 hour exposure. However, both *P. mirifica* and *B. superba* showed potent IGR properties. The result indicated that, *P. mirifica* showed main effect in pupa-adult period in both late 3rd and early 4th instar larve of *Ae. aegypti* and *Cx. quinquefasciatus* whereas *B. superba* showed highest effect in blackpupa period in the either late 3rd larvae of both species of mosquito. The results were reverse for the early 4th instar larvae of *Ae. aegypti* and *Cx. quinquefasciatus* whereas the main effect was appeared in the pupa-adult category. The overall results concluded that *T. peruviana* showed high larvicidal activity whereas *P. mirifica* and *B. superba* seemed to exhibit the juvenile hormone type activity which resulted in abnormal death at various stages of development.

**Oral presentations in:** Joint International Tropical Medicine Meeting 2004, Ambassador Hotel, Bangkok, Thailand, 29 November-1 December 2004.

# SUSCEPTIBILITY OF TWO KARYOTYPIC FORMS OF *ANOPHELES ACONITUS* (DIPTERA: CULICIDAE) TO *PLASMODIUM FALCIPARUM* AND *P. VIVAX*

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*Key words : karyotypic form,* Anopheles aconitus, Plasmodium falciparum, P. vivax

**FOUR** laboratory-raised colonies of two karyotypic forms of *Anopheles aconitus, ie,* Form B (Chiang Mai and Phet Buri strains) and C (Chiang mai and Mae Hong Son strains), were experimentally infected with *Plasmodium falciparum* and *P. vivax* using an artificial membrane feeding technique and dissected 8 and 12 days after feeding for oocyst and sporozoite rates, respectively. The results revealed that *An. aconitus* Form B and C were susceptibile to *P. falciparum* and *P. vivax, ie, Form B (Chiang Mai ad Phet Buri strains/ P. falciparum* and *P. vivax*) and Form C (Chiang Mai and Mae Hong Son strains/ *P. vivax*). Comparative statistical analyses of the oocysts per infected midgut and sporozoite rates among all strains of *An. aconitus* Form B and C the ingroup control vectors, *An. minimus* A and C, exhibitied mostly no significant differences, confirming the high potential vector of the two *Plasmodium* species. The sporozoite-like crystals found in the median lobe of the salivary glands, which could be a misleading factor in the identification of true sporozoites in salivary glands were found in both *An. aconitus* Form B and C.

**Poster presentations in:** Joint International Tropical Medicine Meeting 2004, Ambassador Hotel, Bangkok, Thailand, 29 November-1 December 2004.

# LABORATORY COLONIZATION OF *AEDES LINEATOPENNIS*

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*Key words:* Aedes lineatopennis, *colonization*

***AEDES LINEATOPENNIS,*** a species member of subgenous *Neomelaniconion,* can be colonized for more than 10 successive generations from 30 egg batches of wild-caught femeles. The oviposited eggs need to be incubated in a moisture chamber at least 7 days for the complete embryonation, and following immersion of these eggs in the 0.25-2% hay-fermented water, egg hatching is stimulated of which 61-66% hatched. Larvae are easily reared in 0.25-1% hay-fermented water and provided with suspended powder of equal weight of wheat germ, dry yeast, and oatmeal as the food. Larval development was complete 4-6 days. The pupal stage lasted 3-4 days and nearly all pupae reached the adult stage (87-91%). The adults had to mate artificially and 5-day-old male was proven to be the best age for induced copulation. Three to five-day-old females kept in a paper cup were fed easily on anaesthetized golden hamster that was placed on the top-screen. The average number of egg per gravid female was 63.56 ± 22.93. Unfed females and males kept in a paper cup and fed on 5% multivitamin-syrup solution lived up to 43.17 ± 12.63 (9-69) and 15.90 ± 7.24 (2.39) days, respectively, in the insectarium condition of 27 ± 2°C and 70-80% R.H.

**Poster presentations in:** Joint International Tropical Medicine Meeting 2004, Ambassador Hotel, Bangkok, Thailand, 29 November-1 December 2004.

# GENOTYPES AND PHENOTYPES OF SHIGA TOXIN PRODUCING-*ESCHERICHIA COLI* ISOLATED FROM HEALTHY CATTLE IN THAILAND

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**SUMMARY:** Shiga toxin producing-*Escherichia coli* (STEC) has not yet been identified as an important aetiologic agent of human disease in Thailand. To evaluate the potential for STEC to contribute to human disease in Thailand, 139 fecal samples were collected from healthy cattle from five different provinces and analysed by genotypic and phenotypic methods for STEC. Of 139 samples, 27 (19.4%) were positive for *stx1* and/or *stx2* by multiplex polymerase chain reaction, or for O157 lipopolysaccharide (LPS) by immunoassay. Isolates positive for *stx* and/or 0157 were subdivided into 49 strains that varied in the presence of the virulence determinants *stx1*$^+$/*stx2*$^+$ (22 strains), *stx2*$^+$ (22 strains), *stx1*$^+$ (4 strains), and O157 LPS (1 strain). Within these 49 distinguishable strains, other virulence determinants varied as follows: *hlyA*$^+$ (77.6%), *eae*+ and *tir*$^+$ (4.1%), and *katP*$^+$ (6.12%). The most predominant profile (22 isolates) was *stx1*$^+$ /*stx2*$^+$, *eae*ù, *tir*ù, *etpD*ù, *hlyA*$^+$, *katP*ù. For further characterization of the isolated strains by two molecular typing assays, plasmid profiles and ERIC PCR were performed. The results suggest that the genetic and phenotypic profiles of STEC associated with human disease are not prevalent at this time in cattle in Thailand.

**Published in:** *J Infect* 2004;48:149-60.

# STRONG LINKAGE DISEQUILIBRIUM OF A HBE VARIANT WITH THE (AT)(9)(T)(5) REPEAT IN THE BP1 BINDING SITE UPSTREAM OF THE BETA-GLOBIN GENE IN THE THAI POPULATION

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**A** binding site for the repressor protein BP1, which contains a tandem (AT)(x)(T)(y) repeat, is located approximately 530 bp 5' to the human beta-globin gene (HBB). There is accumulating evidence that BP1 binds to the (AT)(9)(T)(5) allele more strongly than to other alleles, thereby reducing the expression of HBB. In this study, we investigated polymorphisms in the (AT)(x)(T)(y) repeat in 57 individuals living in Thailand, including three homozygotes for the hemoglobin E variant (HbE; (beta)26Glu->Lys), 22 heterozygotes, and 32 normal homozygotes. We found that (AT)(9)(T)(5) and (AT)(7)(T)(7) alleles were predominant in the studied population and that the HbE variant is in strong linkage disequilibrium with the (AT)(9)(T)(5) allele, which can explain why the beta(E) chain is inefficiently synthesized compared to the normal beta(A) chain. Moreover, the mildness of the HbE disease compared to other hemoglobinopathies in Thai may be due, in part, to the presence of the (AT)(9)(T)(5) repeat on the HbE chromosome. In addition, a novel (AC)(n) polymorphism adjacent to the (AT)(x)(T)(y) repeat (i.e., (AC)(3)(AT)(7)(T)(5)) was found through the variation screening in this study.

**Published in:** *J Hum Genet* 2004; Nov 18

# EXTENDED LINKAGE DISEQUILIBRIUM SURROUNDING THE HEMOGLOBIN E VARIANT DUE TO MALARIAL

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**THE** hemoglobin E variant (HbE; (beta)26Glu—>Lys) is concentrated in parts of Southeast Asia where malaria is endemic, and HbE carrier status has been shown to confer some protection against Plasmodium falciparum malaria. To examine the effect of natural selection on the pattern of linkage disequilibrium (LD) and to infer the evolutionary history of the HbE variant, we analyzed biallelic markers surrounding the HbE variant in a Thai population. Pairwise LD analysis of HbE and 43 surrounding biallelic markers revealed LD of HbE extending beyond 100 kb, whereas no LD was observed between non-HbE variants and the same markers. The inferred haplotype network suggests a single origin of the HbE variant in the Thai population. Forward-in-time computer simulations under a variety of selection models indicate that the HbE variant arose 1,240-4,440 years ago. These results support the conjecture that the HbE mutation occurred recently, and the allele frequency has increased rapidly. Our study provides another clear demonstration that a high-resolution LD map across the human genome can detect recent variants that have been subjected to positive selection.

**Published in:** *Am J Hum Genet* 2004; 74(6):1198-208.

# THE USE OF FLOW CYTOMETRY AS A DIAGNOSTIC TEST FOR MALARIA PARASITES

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**A** total of 453 clinical blood samples were determined for malaria parasites by flow cytometric assay (FCM) and reagents from Sysmex Corporation, Japan. In this study, the FCM greatly simplified and accelerated parasite detection, with a sensitivity of 91.26%, specificity of 86.28% and accuracy of 87.42%. Overall, the parasite counts by flow cytometric measurement correlated well with the parasitemia measured by microscopic assay (regression coefficient = 0.9409). The detection limit was 0.05-0.1% parasitemia.

No evidence of malaria parasites in either blood donor volunteers or other disease patients groups was determined by FCM. However, 48 samples, who had been treated with antimalarial drugs and whose parasite microscopic counts were negative, showed false-positive results. When the data of these 48 samples were analyzed, they were found to have high levels of reticulocytes, ranging from 2.0-18.9%. This finding suggested that a high reticulocyte concentration in the blood may interfere with the performance of the FCM. Further improvement, by eliminating this interference, will make the FCM one of the most promising tests for malaria diagnosis.

**Published in:** *Southeast Asian J Trop Med Public Health* 2004;35(3):552-9.

# HUMAN GENES ASSOCIATED WITH SUSCEPTIBILITY TO SEVERE AND CEREBRAL MALARIA IN THAI POPULATION

**Jintana Patarapotikul[1], Hathairad Hananantachai[1], Jun Ohashi[2], Izumi Naka[2], Kazuya Omi[2], Naowarut Dechkum[1], Pornlada Nuchnoi[1], Sornchai Looareesuwan[1], Katsushi Tokunaga[2]**

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**CLINICAL** manifestation of patients infected with *Plasmodium falciparum* varies from mild with a fever to severe complicated with hypoglycemia, respiratory distress, pneumoedema, renal failure and cerebral involvement. The cause that determines the outcome of the disease has not been known. It could involve factors concerning the host, parasite and the environment. Here, we analyze the genetics of human host predisposing to severe malaria in Thai population. We focus our analysis to the genes involved in immune regulation since un-optimized immune response to the parasite might be responsible for the pathogenesis of malaria. Samples of 475 adult patients from northwestern of Thailand were analyzed. They were categorized into 3 groups; mild malaria (n=203), non-cerebral severe malaria (n=164) and cerebral malaria (n=108). Human leucocyte antigen (HLA) for class I and class II were examined but non of them showed significant association. We then further analyzed genes of TNF- ((-1031T/C, -863C/A, -857C/T and -308G/A), TNF receptor2(196M/R), ICAM-1 (29K>M), IL-3(*–16T/C*), IL-4(*-590C/T*), IL-10 (*-1082G/A*) , IL-13 (*–1055C/T*), IFN- (*+874T/A*), MIP1-a(954C/T, 1245A/G, 1728C/G and 1771A/G), MCP-1(-2518A/G, -2348G/C, 2158C/T, -2076A/T, -2072T/C, +764C/G), iNOS(long form CCTTT microsatellite at promoter), Fc gamma receptor IIA(*131H/R*), IIIA(*176V*), IIIB(*NA2/NA1*),IP-10, Groa, Caspase 12, and CD36 receptor (12 TG repeats in intron 3) which involves the cytoadherence of the parasite. However, not all of them are associated with severe or cerebral malaria. Genes that show association are IL-13, iNOS, FcR IIA, IIIB and CD36. Our result demonstrates different set of susceptibility genes to malaria in Thai population reflecting our own evolution to fight with malaria.

**Presented at:** JITMM 2004 meeting , 29 Nov-1 Dec at Ambassador Hotel, Bangkok, Thailand

# MALARIA VACCINE

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**MALARIA** is by far the world's most important tropical parasitic diseases with 300 -500 million clinical cases and about 1.1 million deaths each year. The disease is caused by infection with the protozoan parasite of *Plasmodium*. There are 4 species that can infect human. They are; *P. falciparum, P. vivax, P. malariae and P. ovale* where the first two are the most commonly found for the clinical cases of malaria. However, only *P. falciparum* is found to be a major cause of severe or cerebral malaria leading to death. Therefore, most of the effort is concentrated to research and development of the vaccine against this type of malaria. Here malaria vaccine feasibility and failure of conventional vaccine development for malaria will be reviewed before summarizing the approaches for vaccine development. Finally, malaria vaccines currently under development and their clinical trial will be summarized.

**Presented at:** the shortcourse on " Vaccination in Tomorrow's Society" organized by Infectious diseases unit, Department of Medicine, Faculty of Medicine, Chulalongkorn university during 22-23 January 2004 at Tawannaramada Hotel, Bangkok, Thailand.

# CHARACTERIZATION OF LYMPHOCYTE IN DENGUE HEMORRHAGIC FEVER COMPARED WITH DENGUE-LIKE SYNDROME

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THE blood samples from 49 DHF, 25 DF, and 26 DLS were used to demonstrate atypical lymphocyte count and cellular immune activation, and to evaluate the proportion of CD4+, CD8+, CD19+, CD69+, CD87+ and TDT+ cells during the acute phase of dengue illness, by flow cytometry. The statistical methods used were the ttest, ANOVA, Pearson's correlation test and the receiver operating characteristic (ROC) curve. The results revealed that the mean number of total atypical lymphocytes was higher in patients with DHF (916.1±685.6 cells/µl) than in those with DLS (310.5±181.4 cells/µl, $p<0.05$), and patients with DF had higher atypical lymphocytes (876.2±801.9 cells/µl) than DLS (310.5±181.4 cells/µl, $p<0.05$), but there were no differences between counts in patients with DHF and DF. In a ROC plot of the atypical lymphocyte, the selected cut-off value was 10 because it gave good sensitivity and specificity (50% and 86%). The mean percentage of CD4+ T cells was significantly reduced in DHF patients, but not significantly different in DHF patients compared with DF and DLS patients. The mean absolute count of CD19+ B cells in DHF (615±577 cells/µl) and DF (478±369 cells/µl) was significantly higher than DLS (246±169 cells/µl, $p<0.05$). A CD19 count of  15% or 20% could distinguish DF/DHF from DLS, with a sensitivity of 69% and specificity of 50% if the CD19 was  15%, and a sensitivity of 49% and specificity of 85% if the CD19 was  20%. The atypical lymphocytes, CD19+ B lymphocytes and CD69+ lymphocytes had significant correlation coefficients r=0.403 and –0.241, respectively. The atypical lymphocyte had a linear positive correlation with the CD19+ B lymphocyte and a negative correlation with the CD69+ lymphocyte, at =0.01. The percent of cells expressing CD69 was more increased on CD8+ T cells than CD4+ T cells, and CD19+ B cells, respectively. However the absolute count of CD69 expressed on all lymphocytes was higher than the absolute count of CD69 on total B and T lymphocytes.

The atypical lymphocyte cell could not be differentiated from the lymphocyte by morphology only, but perhaps from NK cells. Further studies are needed to elucidate the roles of NK cells in the pathogenesis of dengue viral infection.

**Poster presented at:** Joint International Tropical Medicine Meeting 2004, Ambassador Hotel, Bangkok, Thailand, 29 Novermber-1 December 2004

# IDENTIFICATION OF DENGUE SEROTYPES ALONG THE THAI-LAOS BORDER USING THE NASBA TECHNIQUE

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IN this study, the detection of dengue serotypes was determined by NASBA technique. The samples were 402 probable DF/DHF patients and 171 students, aged 2-15 years and living in Nhong Kai, Nakhorn Phanom, and Mukdahan provinces. Data were collected from June to September 2002. The samples were tested by Combo Q Check test kit, enzyme-linked immunosorbent assay (ELISA), polymerase chain reaction (PCR) and nucleic acid sequence-based amplification (NASBA). Statistical analyses used were descriptive statistics, Cochran's Q test, McNemar test, and Kappa. Four serotypes of dengue virus were found in 2 provincial hospitals, except in Mukdahan Provincial Hospital, where only dengue virus serotype 2 was found. Mainly, dengue

virus infections were due to dengue 2, by PCR and NASBA. There was excellent correlation in determination of dengue serotypes between PCR and NASBA (Cochran' s Q test, P = 0.065, N = 78), while the positive cases determined by ELISA were more than those determined by Combo Q Check test (McNemar test, P= 0.02, N=78).

When compared to the PCR method, the sensitivities of NASBA by dengue 1-4 were 100, 100, 88.89, and 100%, respectively, while the specificities of NASBA by dengue 1-4 were 100, 99.32, 100, and 100%, respectively. For serotyping, NASBA showed similar specificity and sensitivity to PCR (= 0.97), was also rapid and used only a heating block and water bath. Therefore, the NASBA technique was more suitable in the field than PCR.

**Poster presented at:** American Society of Tropical Medicine and Hygiene 53rd Annual Meeting 7-11 November 2004

## DETECTION OF DENGUE VIRAL RNA IN MOSQUITOES (*AEDES* SP.) BY NUCLEIC ACID SEQUENCE-BASED AMPLIFICATION (NASBA) AND REVERSE TRANSCRIPTASE-POLYMERASE CHAIN REACTION (RT-PCR)

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◎ **VIROLOGIC** surveillance for dengue viruses has been used as an early warning system to predict outbreaks. In this study, the NASBA technique was used to detect serotypes specific of dengue viruses in artificially-infected and in field-caught female adult *Aedes* mosquitoes, which were compared with the RT-PCR technique. In laboratory experiments, NASBA could detect dengue virus serotypes 2 and 4 below 1 PFU/ml, which was more sensitive than RT-PCR, but this technique was as sensitive as RT-PCR when detecting dengue virus serotypes 1 and 3. Most dengue viruses were found at the thorax of the mosquitoes at 0, 7, and 14 days after inoculation with dengue virus serotype 2.

In the field, female adult *Aedes* mosquitoes were collected in the rainy season (June-August, 2002) and the dry season (April, 2003) in Nong Khai Province. These mosquitoes were caught from selected dengue epidemic areas and assayed by NASBA, compared with RT-PCR. From 630 mosquito samples, viral infection rates were 1.61% and 1.13% for NASBA and RT-PCR detection, respectively. The results showed the mosquitoes were infected only with dengue virus serotypes 1 and 2. The sensitivity and specificity of NASBA when compared with PCR were 100% and 99.52%, respectively. The sensitivities of NASBA for two dengue virus serotypes were 100%, whereas the specificities were 99.68% and 99.84% for serotypes 1 and 2, respectively. For serotyping, NASBA showed similar sensitivity and specificity to RT-PCR ( = 0.70). These results indicate that the NASBA assay is another tool for the surveillance of infected mosquitoes that is useful for decreasing the dengue problem.

**Presented at:** Joint International Tropical Medicine Meeting 2004, Ambassador Hotel, Bangkok, Thailand, 29 Novermber-1 December 2004

## SALMONELLAE ENTEROTOXIN GENE AND ENTEROTOXIN IN FOOD AND CLINICAL ISOLATES

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◎ **THIS** study compared enterotoxin gene and it's product in salmonellae isolates from food (30) and clinical (33) samples. All isolates could be grouped into 13 serovars. Existence of the *Salmonella* enterotoxin gene (*stn*) was detected by polymerase chain reaction (PCR). The PCR products of 260-bp were synthesized from specific primers

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**Presented at:** Joint International Tropical Medicine Meeting 2004, Ambassador Hotel, Bangkok, Thailand 29 November-1 December 2004

designed from the *stn* gene. The presence of enterotoxin was detected by determining the cytopathic effect (CPE) of the concentrated cell free supernatants (CCFS) on the Chinese hamster ovary suspension-adapted (CHO-S) cells. CCFS of *V. cholerae* O17SR and *E. coli* DH5 were used as positive and negative controls, respectively. The results demonstrated that all 63 salmonellae isolates in this study contain *stn* gene, but only 12 of the 30 food isolates (40%), and 15 of the 33 clinical isolates (45.5%), showed CPE on the cells. No significant difference in enterotoxin production, between the food and clinical isolates ($p > 0.05$), was found. As mentioned the *stn* gene exists in all *S. enterica* isolates, but only 43% of salmonellae isolates from both groups showed enterotoxin biological activity, as tested by CHO cell elongation assay. The missing phenotypical toxicity among genotypically *stn*-positive isolates indicated that some unknown environmental signals might influence *stn* gene function.

## COMPARISON OF DIRECT IMMUNOFLUORESCENT ANTIBODY TEST AND SABIN-FELDMAN DYE TEST FOR DETECTION OF *TOXOPLASMA GONDII* ANTIBODY IN THAI PREGNANT WOMEN

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THE aim of this study is to determine the specific IgG antibody for *Toxoplasma gondii* in pregnant Thai women by IFAT, using formalin-fixed whole tachyzoites and comparing the sensitivity and specificity with those of the Sabin-Feldman dye test (SFDT). Blood samples were collected from 189 pregnant Thai women, who came for their first visit at the antenatal clinic of Rajavithi Hospital from March to May 2003. The result of antibody measurement from the indirect fluorescent test showed 66.6% sensitivity and 95.9% specificity, when compared with Sabin-Feldman dye test. IFAT is not time-consuming, easy to perform, and formalin-fixed whole antigens can be kept for a long time. IFAT, therefore, is recommended as a selective test, which can be used in laboratories that cannot perform SFDT.

(Funded by Research Fund of the Faculty of Tropical Medicine, Mahidol University)
**Published in:** *Southeast Asian J Trop Med Public Health* 2004; 35(Suppl 1):37-9.

## SENSITIVITY AND SPECIFICITY OF PCR TECHNIQUE TO DETECT *TOXOPLASMA GONDII* IN DOG AND CAT AMNIOTIC FLUID

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THE goal of diagnosing congenital toxoplasmosis is early detection of maternofetal transmission, for early treatment to prevent unwanted sequel. Polymerase chain reaction (PCR) is a method used recently for detecting toxoplasmosis during pregnancy. Amniotic fluid is a clinical specimen used, since it provides a rapid, simple and safe method to obtain accurate results. The advantages of the PCR technique are high sensitivity, specificity and positive predictive value compared with other laboratory methods. To determine the sensitivity, specificity and lower detection limits in our laboratory, amplification of the B1 gene by nested PCR was performed on *Toxoplasma gondii* tachyzoites added to animal amniotic fluid samples. From 48 samples, our technique detected *T.gondii* in 30 out of 41 positive samples, and gave negative results for all the negative samples. The sensitivity for this nested PCR was 73%, the specificity was 100%, and the efficiency of the test was 77.1%. The nested PCR technique is recommended as a diagnostic method for detecting *T.gondii* in suspected congenital toxoplasmosis animals.

(Funded by Royal Golden Jubilee, PhD Program)
**Published in:** *Southeast Asian J Trop Med Public Health* 2004.

# RISK FACTORS AND CLINICAL FEATURES ASSOCIATED WITH SEVERE DENGUE INFECTION IN ADULTS AND CHILDREN DURING THE 2001 EPIDEMIC IN CHONBURI, THAILAND

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**SUMMARY** Objectives Dengue haemorrhagic fever (DHF) is an important cause of morbidity in South-east Asia and used to occur almost exclusively in young children. In recent years, there has been a progressive shift in age-distribution towards older children and adults. We investigated an outbreak in 2001 in both children and adults, in an endemic area of Thailand. Methods Retrospective study of 347 patients with serologically confirmed dengue infection admitted to Chonburi Hospital during an epidemic in 2001. Results A total of 128 (37%) patients had dengue fever (DF) and 219 (63%) had DHF. Patients with DHF were significantly older than patients with DF (11 years vs. 8 years). Clinical bleeding was noted in 124 individuals, both with DF (n = 24) and DHF (n = 100), and significantly more frequently in adults. Twenty-nine (13.2%) of all DHF cases were caused by primary infection. Secondary dengue infection was associated significantly with the development of DHF in children, OR (95% CI) = 3.63 (1.94-6.82), P < 0.0001, but not in adults, OR (95% CI) = 0.6 (0.02-6.04), P = 1. Unusual clinical manifestations were observed in 23 patients: three presented with encephalopathy and 20 with highly elevated liver-enzymes. In the latter group, four patients were icteric and nine had gastrointestinal bleeding. Conclusion These results indicate that DHF in South-east Asia is common in both children and adults. In dengue-endemic countries, dengue should be considered as a differential diagnosis in patients with clinical gastrointestinal bleeding in association with increased liver enzymes.

**Published in:** *Trop Med Int Health* 2004 Sep;9(9):1022-9.

# FREE-LIVING AMOEBA INFECTIONS: RARE BUT FATAL

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**FREE-LIVING** ameba infections, although rare, are recognized as causes of fatal infection in both immunocompetent and immunocompromised persons. *Naegleria fowleri* causes primary amebic meningoencephalitis (PAM), which is a rapid and fulminant central nervous system (CNS) infection in normal hosts. *Acanthamoeba* causes chronic or subacute granulomatous amebic encephalitis (GAE) in immunosuppressive persons. *Balamuthia* also causes GAE, but in competent hosts.

PAM should be considered in all patients with meningoencephalitis, especially if they have a recent history of swimming in fresh water. A clue that suggests the diagnosis is a negative CSF Gram stain finding in a patient with purulent meningitis.

Healthcare providers should be aware of *Acanthamoeba* as a potential pathogen in the HIV-infected patient population. Early diagnosis may allow for prompt intervention and increase a patient's chance of survival.

Clinicians, parasitologists, and pathologists must include free-living amebae in the differential diagnosis of possible pathogenic agents that cause sinusitis and cutaneous nodules or ulcers, with or without CNS involvement, especially when bacteria, fungi, or mycobacteria are not found by smear, biopsy, or culture. Typical motility of trophozoites on fresh examination is a key for diagnosis. Broad pseudopodia movement is typical for *Naegleria*, and it can turn into temporary flagellated form. Spiny cytoplasmic projection or acanthopodia is characteristic of *Acanthamoeba*.

Thoughtful history taking, prompt simple laboratory examination, and awareness can be very rewarding.

**Published in:** The Journal of Tropical Medicine and Parasitology, 2004; 27(1):26-36.

# LEISHMANIASIS IN THAILAND

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**LEISHMANIASIS,** an infectious disease caused by *Leishmania* protozoa parasite, is now endemic in 88 countries in five continents with a total of 350 million people at risk. Thailand is not an endemic area of the disease, nevertheless both cutaneous and visceral leishmaniasis had been reported.

All cutaneous leishmaniasis occurred in Thai workers who return from Middle East, visceral leishmaniasis had been documented in foreigners who came from endemic area as well as Thai exchange workers who had been working there. However, there was the first indigenous case of visceral leishmaniasis reported in 1999.

Thai government has launched the Medical Hub project that offers medical services to foreigners. Thai solders have been sent to Iraq, which is an endemic area of leishmaniasis. Moreover, HIV/AIDS is pandemic in Thailand, therefore leishmaniasis as an opportunistic infection and co-infection should be carefully looked for. For these reasons Thai physicians, paramedical personnel and those in charge of laboratory units should be well prepared and be aware of the disease.

**Oral presentation at:** the Fifth Sir Dorabji Tata Symposium on Leishmaniasis, 10-11 March 2004, Bangalore, India

# BUDISTHSM AND ZOONOSES

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**BUDDHISM** is a major religion and plays a vital role of Thai society. Belief and cultural practices lead to unwanted pet dogs and cats being abandoned in temples where monks are obliged to care for them. It is estimated around 20,000 dogs and 10,000 cats are left in 500 Buddhist temples in Bangkok. The overcrowded conditions makes Buddhist temples as a place at risk of acquiring zoonotic infection.
Rabies and tetanus are important zoonoses, which cause burden to Thai government and need large effort to cope with them. Toxoplasmosis was recently studied from 315 cats and 327 humans in 14 temples, provided strong association between seropositive owners who lived proximity to seropositive cats [OR (95%CI) = 5.43 (1.28-23.04); p=0.01]. Risks were increased in and around temples.

Molecular study on parasitic and other zoonoses are of our interesting research projects. The information gathered from previously and on going studies will determine the potential risks dogs and cats pose as transmitters of zoonoses. This would help generate measures of control and Thai people might more take care of their pets. The way to leave unwanted or stray dogs and cats in Buddhist temples will be reconsidered.

(Funded by Thanat-Molee Khoman Foundation)

**Oral presentation at:** Australian Association of Parasitology, 23-27 September 2004, Perth, Australia)

# SPA, SPRINGS AND SAFETY

**Yaowalark Sukthana[1], Amorn Lekkla[1], Chantira Suthikornchai[1], Paitoon Wanapongse[2], Athasit Vejjajiva[3], Somchai Bovornkitti[3]**

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**NATURAL** mineral water has long been used worldwide for the bathing and health purposes for many thousands years. At present, Thailand is famous for health spa and natural hot springs among local people and tourists. Since, there may be possible risks of exposure to harmful agents we, therefore, studied hazardous pollutants in 57 sites of natural hot springs from 11 provinces in Northern, Central, Eastern and Southern Thailand. Pathogenic free-living amoebae of the genera *Naegleria* and *Acanthamoeba* which can cause central nervous system infection were found in 26.3% (15/57) and 15.8% (9/57) respectively. Dissolved radon, a soil gas with carcinogenic

properties, was present in nearly all hot springs sites with concentration ranging from 0.87- 76,527 Becquerels/cubic meter. They were 5 water samples in which radon concentration exceeded the safety limit for drinking. *Legionella pneumoniphila*, serogroups 1,3, 5, 6, 7 10 and 13 were found in samples from 71.9% (41/57) of studied sites. Since spa and natural springs are popular tourist attraction, the health authorities concerned should be aware of those possible hazards and provide tactful measures and guidelines to ensure safety without causing undue alarm to foreign and Thai tourist.

(Financially supported by Thanat-Molee Khoman Foundation)

**Oral Presentation at:** Joint International Tropical Medicine Meeting, Bangkok, 29 November – 1 December 2004

## FREE-LIVING AMOEBA CONTAMINATION IN NATURAL HOT SPRING IN THAILAND

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**THERMO** tolerant free-living amoeba, *Naegleria* spp. and *Acanthamoeba* spp. contaminated in natural hot spring in Thailand were carried out from 13 provinces. The temperature of hot springs water were vary from 28 °C- 65 °C and pH form 6-8. We found that 38.24 % (26/68) of water samples were positive, *Acanthamoeba* was 13.24% (9/68) whilst *Naegleria* was 35.29% (24/68).

Contaminated by free-living amoeba in Natural hot springs may pose a significant health risk to people who use such water as recreation activities.

(Funded by Thanat-Molee Khoman Foundation)

**Poster presentation at:** Joint International Tropical Medicine Meeting, Bangkok, Thailand, 29 November – 1 December 2004

## PROTOZOAL CONTAMINATION OF WATER USED IN THAI FROZEN FOOD INDUSTRY

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**WATER** is involved in nearly all steps of food preparation. If contaminated or improperly treated it may lead to contaminated food products. This study evaluated the prevalence of contamination of water that was used for food preparation. Since protozoal cysts can be found in small number in water, 1,000 liters of either untreated or treated water were filtered through activated carbon block filters (1 mm nominal porosity). Identification of protozoa was performed using specific monoclonal antibodies against *Giardia* and *Cryptosporidium* parasites followed by fluorescence microscopy.

Twelve of 20 untreated water samples (60%) were found to be contaminated by *Giardia* cysts, with an average of 53.33cysts/1,000 L (geometric mean 39.44), whilst 7 samples (35%) were contaminated by *Cryptosporidium* oocysts, with an average of 28.57 oocysts/1,000L (geometric mean 26.92). Three samples of untreated water (15%) were positive for both organisms. In contrast, none of treated water samples was contaminated.

Untreated water is a potential source of food contamination, thus, treated water should be promoted for use in all steps of food preparation in each frozen food industry.

(Funded by Thanat-Molle Khoman Foundation and Faculty of Tropical medicines Research Fund)

**Poster presentation at:** Australia Association of Parasitology, 23-27 September 2004 Perth, Australia, and at Joint International Tropical Medicine Meeting, Bangkok, Thailand, 29 November-1 December 2004

# HUMAN AND CANINE GIARDIASIS IN TEMPLE-RELATED COMMUNITIES IN BANGKOK, THAILAND

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(Funded by The Faculty of Tropical Medicine Research Fund and Bayer Animal Drug Company)

**Poster Presentation in:** Australia Association of Parasitology, Perth, Australia, 21-26 September 2004 and oral presentation in Joint International Tropical Medicine Meeting, Bangkok, Thailand, 29 November – 1 December 2004

◎ ***GIARDIA DUODENALIS*** is a flagellated protozoan that inhabits the small intestine in man and other mammals. In Thailand, religious and cultural practices lead to unwanted pet dogs being abandoned in temples where monks are obliged to care for them. The close relationship shared with dogs coupled with overcrowded conditions place monks and the surrounding underdeveloped communities at an increased risk of acquiring *Giardia* from dogs.

Fecal samples were collected from 162 humans and 200 dogs from 18 different temples in Bangkok and communities in the surrounding areas. Both human and dog stool samples were examined for *Giardia* using zinc sulfate flotation. The prevalence of *Giardia* in dogs was found to be 9% while in humans was 3%. However, when randomized 100 dog and 80 human stool samples by PCR technique, the prevalence of *Giardia* was 75% in dogs and 60% in humans respectively. Twenty samples of positive PCR were selected and tested by immunofluorescence to support PCR result. All microscopy positive for *Giardia* were genotyped, the majority of dog population were placed into Assemblage A following by Assemblage B,D and C respectively, while human isolates were placed within Assemblage A and B. Therefore, dogs in temple communities posing significant zoonotic risk to humans with regards to transmission of *Giardia*, especially Assemblage A. Multi-variate risk factor analysis revealed that dogs belonged to temples and also dogs allowed outside the house into the temples compound significantly more likely to be infected with *Giardia*.

# HAZARD POLLUTANTS IN NATURAL HOT SPRINGS, LOPBURI PROVINCE, THAILAND

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◎ **WATER** samples from 2 sites natural hot springs from Lop Buri Province were collected to examine possible hazardous pollutant contamination. The finding revealed high levels of dissolved radon gas. Under light microscopy by fresh direct smear and trichrome staining *Naegleria* and *Acanthamoeba* were found in both samples. No *Legionella* organism was isolated from any specimens.

**Published in:** *Int Med J Thai* 2004;20(3):211- 4.

# ESTABLISHED DOUBLE ANTIBODY ELISA METHOD FOR DETECTION OF PATHOGENIC PROTOZOAL ANTIGENS IN THE FECES

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THE antigen of *Giardia intestinalis*, *Entamoeba histilytica* and *Blastocystis hominis* will be prepared from axenic cultures. Two each of rabbits and each of goats were immunized with individual extract. The stimulated antibodies were examined by indirect enzyme-linked immunosorbent assay (Sandwich ELISA). The secondary antibody were collected from immunized goats, which reacted with *G. intestinalis*, *E. histolytica* and *B. hominis* in fecal samples. The fecal samples were performed in four groups; confermed cases using microscopic examination of giardiasis, amoebiasis and blastocystosis; stools containing other parasites; patients after anti-protozoal therapy and healthy subjects. The specificity and sensitivity of the tests were compared with those from commercial test kits and microscopic examination, which was a gold standard. Comparison between microscopic examination and Sandwich ELISA, sensitivity of the ELISA used to *G. intestinalis*, *E. histolytica* and *B. hominis* showed 42.6%, 43.6% and 90% respectively. Spesificity of the ELISA showed 81.6%, 84.2% and 78.9% respectively. Sandwich ELISA showed superior sensitivity and specificity to test kits of *G. intestinalis* and *E. histolytica* but both interpretations of the tests were not much different.

**Reported to:** National Science and Technology Development Agency (NDTDA) 30 September 2004)

# LABORATORY DIAGNOSIS OF PATHOGENIC FREE-LIVING AMOEBAE: MICROSCOPIC FINDINGS FROM PATIENT'S SPECIMENS AND CULTURES

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THE first case of dual infections with *Naegleria* spp. and *Acanthamoeba* spp. in a symptomatic patient is reported. Identification and differentiation of free-living amoebae was performed from nasal exudates and sputum specimens. The typical characters of *Naegleria* spp. and *Acanthamoeba* spp. are described. *Naegleria* and *Acanthamoeba* trophozoites were detected from fresh observation using a compound microscope and phase-contrast optics and the characters of the amoeba trophozoites could be differentiated from leukocytes by Giemsa stain. Enflagellation was the criterion used for differentiating *Naegleria* spp. from *Acanthamoeba* spp. The flagellate form of *Naegleria* spp. was demonstrated after enflagellation. Samples of nasal exudates were inoculated into egg slant medium for cultivation; flagellate stages of *Naegleria* could be successfully maintained in the medium for several months for further study. For treatment follow-up, a comparison of fresh observation, staining, and tissue culture methods, for the detection of pathogenic free-living amoebae after drug therapy, was set up. Giemsa, Gram-Chromotrope, and Thomas stains, were used. The amoeba trophozoites were inoculated into Hep-2 and primary chicken kidney cells, and their survival was determined within 24 hours. Of the three methods, tissue culture was the best for detecting the survival of pathogenic free-living amoebae after drug therapy. The amoeba trophozoites were detected within 24 hours post-inoculation and the typical characters of amoeba trophozoites from culture were demonstrated by fresh observation. Although the survival of amoeba trophozoites could not be determined by staining methods, the typical characters of amoeba trophozoites and ingested reticulocytes were demonstrated by Thomas and gram-chromotrope stains. In conclusion, the most appropriate method for diagnosis of pathogenic free-living amoebae is fresh observation. Staining methods are valuable for the confirmation of characteristic details and tissue culture is recommended for the detection of amoeba trophozoites after drug therapy.

**Oral Presentation at:** Joint International Tropical Medicine Meeting, Banakok, 29 November – 1 December 2004.

# OBSERVATION OF INTRACELLULAR PROTOZOAN DEVELOPMENT BY TISSUE CULTURE ON COVER GLASSES AND DETECTION BY FRESH OBSERVATION AND STAINING METHODS

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**Poster Presentation at:** Joint International Tropical Medicine Meeting, Banakok, 29 November – 1 December 2004.

◎ ***ISOSPORA BELLI,*** *Cryptosporidium parvum* sporozoites and *Microsporidial* spores were infected into culture cells. The developmental stages of these intracellular protozoa were described after the fresh observation and staining of infected cells on cover glasses. Paraffin tissue section was performed and compared to cover glass staining. Fresh observation was more advantages for the observation of the movement of *I. belli* merozoites but the development of merogony of *Cryptosporidium* could not be notified by fresh observation. The merogony stages of *I. belli* from paraffin tissue sections were not clear, compared to cover glass staining but the trophozoites of *Cryptosporidium* were clearly demonstrated by paraffin tissue sections. The typical characters of belt-like stripes of *Microsporidial* spores from culture were clearly observed from cover glass staining. In conclusion, cover glass staining could be used for an alternative method for the detection of intracellular protozoa from cultures. However, the proper staining methods should be selected for each protozoan parasite.

# MICROSCOPIC AND ULTRASTRUCTURAL FINDINGS OF PROTOZOAN INFECTIONS

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**Presented at:** The 8th Asia-Pacific Conference on Electron Microscopy (8APEM) June 7th – 11th, 2004, Kanazawa, Japan.

◎ **MICROSCOPIC** examination is still a diagnostic tool for identification of protozoan parasites from patients' specimens. The reliability of diagnosis depends on the detection of organisms and demonstration of their typical characters. The uncommon protozoa have been described and discussed, according to their microscopic and ultrastructural structures. Large protozoan, *Isospora belli* oocysts are quite characteristics that could be easily detected in fecal materials. However, in mild infection it is necessary to identify by staining method. On the contrary, *Microsporidium* spores are too small to detect by simple smear preparation but they could be identified and special stain and confirmed by transmission electron microscope as the gold standard. Amphizoic amoebae which are human pathogens, named *Naegleria* and *Acanthamoeba*. Both of them cause brain symptoms. However, the morphology looks similar to macrophage. Therefore, it is quite difficult to differentiate from white blood cells. The observation of their movement and the characteristics of pseudopodia are important criteria. Out findings showed the typical characters of these free-living amoebae from nasal exudates of a symptomatic patient by both fresh preparation and staining methods including scanning and transmission electron microscope. This is the first report of early detection of *Naegleria* and *Acanthamoeba* infection. All information was reported herein.

# IDENTIFICATION OF HUMAN MALARIA PARASITES AND DETECTION OF MIXED INFECTION IN THAI PATIENTS BY NESTED PCR

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**THE** species-specific nested PCR previously described by Snounou and others for detecting the four species of human malaria parasites is evaluated in the current study testing 40 blood samples from malaria patients admitted during July-September,2003 at the Hospital for Tropical diseases, Faculty of Tropical Medicine, Mahidol University, Thailand. Parasite DNA of each blood sample was extracted and purified by using QIAmp DNA blood kits. The nested PCR was performed by using genus-specific primers for the first PCR cycle and species-specific primers for the second cycle. Thin and thick smears were also made, stained with Giemsa and examined by expert microscopists. Only one out of 40 samples (2.5%) was identified as *Plasmodium malariae* infection by both microscopy and nested PCR. Twenty blood samples (50%) were identified as *Plasmodium falciparum* infection by both methods. However, 19 blood samples (47.5%) were reported as *Plasmodium vivax* infections by microscopic method whereas nested PCR could detect a mixed infection of *Plasmodium vivax* and *Plasmodium falciparum* in one sample which taken from a young girl with 8 trophozoites of *P. vivax*/200 white blood cells. These results demonstrated that the nested PCR assay surpasses microscopy and also offers a clear advantage in the detection of mixed infections, which is important not only for successful medical treatment but also for the study of malaria epidemiology.

This work was supported by the Commision on High Education, Ministry of Education Of Thailand.

**Published in:** *Southeast Asian J Trop Med Public Health* 2004;35 (Suppl 2):5-9.

# IDENTIFICATION OF *CRYPTOSPORIDIUM PARVUM* GENOTYPE FROM HIV AND NON-HIV FECAL SAMPLES BY PCR

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**IN** this study, specific primers of genotype 1 and 2 were used to identify the *C. parvum* genotypes in fecal samples. A total number of 30 fecal HIV and non-HIV samples of *C. parvum* were examined by microscopic method, comprised of 7 samples from non-HIV children aged between 8 to 12 years, 11 fecal samples from adults with HIV-positive adults and 12 purified oocysts of *C. parvum* from HIV patients. Within this group of infected children, 5 children were infected with genotype 1 while 2 samples were unclassified. In the HIV-positive adult patients, 7 samples were genotype 1, while 4 samples were unclassified. Of the 12 purified oocyst samples, 11 samples were positive for genotype 1, while only 1 purified oocysts sample was unclassified. The unclassified samples observed in our study may belong to other the genotypes and no *C. parvum* genotype 2 were detected in our study population.

This study was funded by Faculty of Tropical Medicine, Mahidol University.

**Published in:** *Southeast Asian J Trop Med Public Health* 2004;35(Suppl 1):30-3.

# GLUTATHIONE-*S*-TRANSFERASES FROM CHLOROQUINE-RESISTANT AND –SENSITIVE STRAINS OF PLASMODIUM FALCIPARUM; WHAT ARE THEIR DIFFERENCES?

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**GLUTATHIONE-S-TRANSFERASES** (GSTs) from chloroquine-resistant (CQR, K1) and–sensitive (CQS, T9/94) strains of *Plasmodium falciparum* were studied. The enzymes from both strains exhibited the optimal pH for enzyme catalysis at pH 7.5 and were stable at the temperature below 60 C. They also showed the highest specific activities toward CDNB and moderate activities to ethacrynic acid (40% of the activity to CDNB) but little or no activity for other substrates. $K_m$ and $V_{max}$ values for CDNB and GSH calculated by Lineweaver-Burk plot from both CQR- and CQS-GSTs were not statistically different ($p<0.05$). However, the GSTs activity from CQR appeared to be significantly higher than that from CQS. Therefore, we proposed that GSTs from both malarial strains are identical in their functional domain but different in level of their gene expression. Furthermore, protein sequence alignment between *P. falciparum* GST and GSTs from other organisms suggested that the malarial enzyme is closely similar to other GSTs in *Sigma, Alpha, Mu* and *Pi* subclasses, probably the most to *Alpha* group. Characterization of the purified malarial GST in detail would reveal more precise classification and more understanding into its role in the malarial detoxification.

**Published in:** *Southeast Asian J Trop Med Public Health* 2004;35:292-9.

# EVALUATION OF DNA EXTRACTION AND PCR METHODS FOR DETECTION OF *ENTEROCYTOZOON BIENEUSI* IN STOOL SPECIMENS

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**EVALUATION** of the sensitivities of three DNA extraction methods, i.e., FTA filter paper, QIAamp stool mini kit and conventional phenol-chloroform method by using specimens with known concentration of *Enterocytozoon bieneusi* spores was performed. FTA filter paper and the QIAamp stool mini kit were the most sensitive methods, which could detect *E. bieneusi* in specimens with a concentration of 800 spores/ml. We also compared 5 previously described PCR methods that use five different primer pairs for the detection of *E. bieneusi* and showed that MSP3/MSP4B and EBIEF1/EBIER1 were the most sensitive primers. Although both sets of primers showed the same sensitivity, MSP3/MSP4B primers can directly provide genotypic information by sequencing. A blind diagnostic test to compare PCR and light microscopy methods for the detection of *E. bieneusi* in stool dpecimens was also conducted. The use of FTA filter paper for DNA extraction together with PCR method using the primer pair MSP3/MSP4B primers showed 100% sensitivity and 100% specificity for the detection of *E. bieneusi* in stool specimens, while the light microscopy method gave a sensitivity of 86.7% and a specificity of 100%.

This work was supported by Thailand-Tropical Diseases Research Programme (T-2)

**Published in:** *Journal of Clinical Microbiology* 2004;42:3490-4.

# MULTIPLEX REAL-TIME PCR USING LIGHTCYCLER FOR MALARIA DIAGNOSIS

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**THE** accurate and rapid diagnosis of malaria is needed for successful medical treatment and the study of malaria epidemiology especially in endemic areas. Many diagnostic methods have been used to detect human malarial parasites such as a microscopic method, rapid diagnostic tests and polymerase chain reaction (PCR), however, these diagnostic methods still have some disadvantages. Therefore, a rapid real-time PCR assay using the LightCycler (Roche Applied Science-RAS) was currently developed for the detection and differentiation of the four species of *Plasmodium* causing human malaria. A genus-specific primer set corresponding to the 18S small subunit rRNA was used to amplify the target and fluorescence resonance energy transfer (FRET) hybridization probes were designed to differentiate species by use of melting curve analysis. The complete assay can be performed in one cuvette within 2 hours. We evaluated 250 specimens of blood collected from Thai patients suspected of having malaria. Parasite DNA of each blood sample was extracted and purified by using High Pure PCR template preparation kit. Real-time PCR was performed by using LightCyCler. Thin and thick smears were also made, stained with Giemsa and examined by expert microscopists. PCR results were compared with microscopic method. Thirty seven specimens were negative whereas 124, 77 and 6 specimens were positive for *P. falciparum, P. vivax* and *P. malariae*, respectively, by both methods. Only one specimen was detected as mixed infection of *P. falciparum* and *P. vivax* by both methods. The multiplex PCR using the LightCycler result showed that 127, 79 and 6 specimens were positive for *P. falciparum*, *P. vivax* and *P. malariae* respectively. Five specimens was reported as mixed infection of *P.falciparum* and *P. vivax* by microscopy but were called 3 *P. falciparum* and 2 *P. vivax* by real time-PCR. This study suggests that real-time PCR is an objective, standardized, sensitive and specific method for the rapid diagnosis of malaria which does not require expertise in blood smear preparation and interpretation.

**Oral Presentation in:** Joint International Tropical Medicine Meeting 2004, 29 November-1 December 2004 at Ambassador Hotel, Bangkok, Thailand.

# MOLECULAR CHARACTERIZATION OF *ENTEROCYTOZOON BIENEUSI* IN HIV-INFECTED PATIENTS, THAILAND

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***ENTEROCYTOZOON BIENEUSI*** is the microsporidian species most frequently found in human infection. It is responsible for chronic diarrhea in immuonocompromised patients, especially patients infected with human immunodeficiency virus. This species has also been found in other mammals, pets, poultry, and wildlife. Phylogenetic analysis of the internal transcribes spacer region of rDNA sequence revealed the close linkage between human and animal isolates of *E. bieneusi*. It has been suggested the possibility of zoonotic transmission of *E. bieneusi*. The report of animal isolates identified in human fecal samples emphasized animal-to-human transmission and source of *E. bieneusi*. Our study aimed to explore the possibility of zoonotic potential of *E. bieneusi*. Forty-five microsporidia positive fecal specimens were examined by molecular method for *E.bieneusi*. A PCR protocol was used to amplified 508-bp fragment of ITS region of the rRNA gene using primer MSP3/MSP4B. Forty two-PCR products from *E. bieneusi* positive samples were sequenced. Multiple alignments of these sequences identified 12 genotypes of *E. bieneusi*, 6 genotypes were firstly reported here. Sixteen were human genotype which 11 were human Genotype D and 5 were Peru genotype. Some of the isolates were identical to swine, pig, and muskrat genotypes. The results of this study indicate that animal-to-human might be one of the mode of transmission of *E. bieneusi*.

**Oral Presentation in:** Joint International Tropical Medicine Meeting 2004, 29 November-1 December 2004 at Ambassador Hotel, Bangkok, Thailand.

# THE HEALTH BELIEF MODEL AND FACTORS RELATING TO POTENTIAL USE OF A VACCINE FOR SHIGELLOSIS IN KAENG KOI DISTRICT, SARABURI PROVINCE, THAILAND

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**SHIGELLOSIS** is an important cause of morbidity and mortality throughout the world. Approximately, 1.1 million deaths occur a year due to this disease, making it the fourth leading cause of mortality worldwide. This paper explores local interest in and potential use of a vaccine for shigellosis in Thailand where *Shigella* poses an important public-health concern. Data for this study were collected during June-November 2002 from 522 subjects surveyed using a sociobehavioural questionnaire in Kaeng Koi district in central Thailand. The community demand and likely use of a vaccine were examined in relation to the Health Belief Model, which provides analytical constructs for investigating the multiple issues of local readiness to accept and access a new vaccine. As the key outcome variable, most respondents showed interest in receiving a vaccine against dysentery which they thought would provide useful protection against the disease. However, there was only a moderate number who perceived dysentery as serious and themselves as susceptible to it, although it was perceived to cause some burden to and additional expense for families. Most people identified a number of groups who were thought to be especially vulnerable to dysentery, such as the elderly, pre-school, and school-age children, and poor labourers, Other outcomes of the study included the identification of acceptable and convenient sites for its delivery, such as government health clinics and private clinics, and respected sources for information about the vaccine, such as health clinic personnel and community health volunteers. This information suggests that components of the Health Belief Model may be useful in identifying community acceptance of a vaccine and the means of introducing it. This health information is important for planning and implementing vaccine programmes.

**Published in:** *J Health Popul Nutr* 2004,22:170-81.

# RISK FACTORS FOR TUBERCULOSIS INFECTION AMONG HOUSEHOLD CONTACTS IN BANGKOK, THAILAND

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**A** cross-sectional study was conducted to determine the prevalence of tuberculosis infection and risk factors for tuberculosis infection among household contacts aged less than 15 years in Bangkok, Thailand, between August 2002 and September 2003. During the study period, 342 index cases with sputum smear positive pulmonary tuberculosis patients were recruited into the study and their 500 household contacts aged under 15 year were identified. The prevalence of tuberculosis infection among household contacts was found to be 47.80% (95%CI=43.41-52.19). In multivariate analysis, a generalized estimation equation (GEE) was used to determine the risk factors for tuberculosis infection among household contacts. The results indicated that the risk of tuberculosis infection was significantly associated with close contact (adjusted OR=3.31, 95%CI=1.46-7.45), exposure to female index case (adjusted OR=2.75, 95%CI=1.25-6.08), exposure to mother with tuberculosis (adjusted OR=3.82, 95%CI=1.44-10.14), exposure to father with tuberculosis (adjusted OR=2.55, 95%CI=1.19-5.46), exposure to index case with cavitation on chest radiograph (adjusted OR = 4.43, 95%CI=2.43-8.05), exposure to index case with 3+ sputum smear grade

(adjusted OR=3.85, 95%CI=1.92-7.70), and living in crowded household (adjusted OR=2.63, 95%CI=1.18-5.85). The distribution of tuberculosis infection and risk factors among contact cases are significant for health care staff in strengthening and implementing tuberculosis control programs in Thailand.

**Published in:** *Southeast Asian J Trop Med Public Health* 2004;35:375-83.

## SEXUAL RISK REDUCTION IN A COHORT OF INJECTING DRUG USERS IN BANGKOK, THAILAND

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**OBJECTIVE:** Interventions to reduce sexual risk behavior among injecting drug users (IDUs) have generally had very modest effects, but almost all such interventions have been conducted within short time frames. This study assessed whether long-term participation in interventions to reduce sexual risk behavior was associated with reduced sexual risk behavior.

METHODS: A total of 806 IDUs participated in the Bangkok HIV Vaccine Trial Preparatory Cohort Study from 1995-1998 and remained in the study for at least 4 follow-up visits (approximately 16 months). Participants received HIV counseling and testing every 4 months and free condoms were provided. Structured interviews including questions on sexual behavior were administered every 4 months.

RESULTS: Approximately 40% of participants reported engaging in unprotected sex (vaginal intercourse without always using a condom) with a regular partner at each study visit, without any decline over time in this behavior. There were declines in the proportions of participants reporting unprotected sex with casual partners and with paid partners (men only) over time, but the declines were confined to the early period of the study. Unprotected sex with casual partners was associated with amphetamine use. Condom use increased substantially among participants who seroconverted for HIV during the study.

CONCLUSIONS: Interventions to reduce sexual risk behavior among HIV-seronegative IDUs over extended periods were no more likely to be effective than shorter interventions. New programs are needed to reduce sexual risk behavior among amphetamine users and among IDUs who are currently seronegative but are engaging in injection risk behaviors and in unprotected sex with regular partners.

**Published in:** *J Acquir Immune Defic Syndr* 2004;37:1170-9.

## EARLY MARKERS OF HIV-1 DISEASE PROGRESSION IN A PROSPECTIVE COHORT OF SEROCONVERTERS IN BANGKOK, THAILAND: IMPLICATIONS FOR VACCINE TRIALS

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**BACKGROUND:** Some candidate HIV-1 vaccines may not prevent HIV-1 infection but may alter the course of disease. Surrogate endpoints based on early laboratory makers in HIV-1-infected persons who are antiretroviral therapy (ART)-naive will be useful for evaluating vaccine efficacy in slowing disease progression (VEp). We examined pretreatment HIV-1 viral loads and CD4 cell counts in recent HIV-1 seroconverters to inform selection of these endpoints.

METHODS: We studied 130 newly HIV-1-infected injection drug users identified from a prospective cohort of initially uninfected persons in Bangkok during 1995 through 1998. We analyzed trends in HIV-1 viral loads and CD4 cell counts as well as progression to the surrogate endpoint, defined as 2 consecutive CD4 cell counts

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of fewer than 350 cells/mm, during 24 months after the first HIV-1 seropositive (FP) visit.

RESULTS: Median HIV-1 RNA copies/mL with interquartile ranges were 43,693 (14,320-94,767) at the FP visit, 46,924 (16,273-104,314) at 6 months, 28,446 (11,292-54,325) at 12 months, and 18,080 (8,713-54,059) at 18 months. HIV-1 viral loads at the FP visit and at 18 months were positively correlated ($r = 0.53$, $P < 0.0001$). Of 130 participants, 12% reached the surrogate endpoint by 6 months, 16% by 12 months, and 27% by 18 months. In Cox regression analyses, HIV-1 viral loads of more than 50,000 copies/mL at the FP visit (hazard ratio [HR] = 2.3, 95% confidence interval [CI]: 1.1-4.8) and first CD4 cell count of 500 or fewer cells/mm (HR = 7.6, 95% CI: 3.2-17.6) were independently associated with faster progression to the surrogate endpoint.

CONCLUSIONS: Participants with high HIV-1 RNA levels and low CD4 cell counts close to the time of seroconversion were more likely to experience early immunologic progression. Approximately one quarter of seroconverters reached the surrogate immunologic endpoint within 18 months of their FP visit and before starting ART, suggesting the utility of this endpoint for analyses of VEp in some ongoing and planned HIV-1 vaccine efficacy trials.

**Published in:** *J Acquir Immune Defic Syndr* 2004;36:853-60.

## HLA CLASS II (DRB1, DQA1 AND DQB1) ALLELE AND HAPLOTYPE FREQUENCIES AMONG HIV-INFECTION DISCORDANT THAI COUPLES

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◎ WE investigated the association of HLA-DRB1, -DQA1 and -DQB1 alleles and haplotypes in 33 Thai HIV discordant couples. A significantly lower frequencies of DRB1*14 (3.0% vs 11.3%, p = 0.048) and DQA1*0103 (0.0% vs 5.63%, p = 0.042) alleles were found in the seropositive individuals when compared with HIV-negative controls. In contrast, there was no significant difference in HLA-DQB1* allele frequencies. The haplotype analysis revealed that DRB1*1501-DQA1*0102-DQB1*0601 (7.6% vs 0.0%, p = 0.002), DRB1*0405-DQA1*0302-DQB1*0401 (7.6% vs 1.3%, p = 0.024) and DRB1*1401-DQA1*0104-DQB1*05031 (6.1% vs 0.0%, p = 0.007) were found to be significantly higher frequencies when compared between HIV seronegative partners and HIV negative controls, but DRB1*1501-DQA1*0102-DQB1*0502 (0.0% vs 8.1%, p = 0.01) was significantly lower. The DRB1*1602-DQA1*0101-DQB1*0502 (4.6% vs 0.0%, p = 0.024) haplotype was found to be significantly higher frequencies in HIV seropositive individuals when compared to HIV negative controls but the DRB1*1502-DQA1*0101-DQB1*0501 (1.5% vs 8.1%, p = 0.049) haplotype was lower.

**Published in:** *Asian Pac J Allergy Immunol* 2004;22:143-51.

# COMPARISON OF BIOLOGICAL SPECIMENS FOR MANGANESE DETERMINATION AMONG HIGHLY EXPOSED WELDERS

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**Published in:** *Southeast Asian J Trop Med Public Health* 2004,35:764-9.

**THIS** research aimed to determine if less invasive biological specimens (other than blood), such as feces and clipped toenails could be used to determine manganese concentrations among occupationally exposed human subjects. In addition to blood samples, which have routinely been used in determining manganese concentration, specimens were collected from welders working at the Electricity Generating Authority of Thailand, Mae Moh Thermal Power Plant, Lampang Province. Manganese concentrations in thest three biological samples were determined by atomic absorption spectrophotometer. Correlations of manganese concentrations among these three biological samples were measured, and found to be rather poor (Pearson's $r < \pm 0.2$, $p > 0.1$ for any pair-wise comparisons). Blood remins the recommended material for biomonitoring manganese concentrations in occupationally exposed subjects.

# SIMULTANEOUS DETERMINATION OF *TRANS,TRANS*-MUCONIC ACID AND S-PHENYLMERCAPTURIC ACID BY HIGH PRESSURE LIQUID CHROMATOGRAPHY AND ITS APPLICATION

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**Published in:** *Southeast Asian J Trop Med Public Health* 2004;35:717-23.

**THE** simultaneous determination of urinary *trans,trans*-muconic acid (*t,t*-MA) and *S*-phenylmercapturic acid (S-PMA) was performed by liquid extraction with ethyl acetate and reversed-phase high performance liquid chromatography (RP-HPLC) on a Hypersil-ODS column using the gradient mobile phase of methanol and 0.0012 N perchloric acid and diode array detection at 205 and 264 nm for S-PMA and t,t-MA, respectively. The rectention times for t,t-MA and S-PMA were 3.8 and 12.3 minutes, respectively, The recoveries of t,t-MA and s-PMA were >97%; between-day precisions were all within 8% RSD (100x SD/mean). The method was applied to analyze the urinary t,t-MA and S-PMA of 59 service station attendants exposed to average benzene concentrations in the air of $0.20 \pm 0.18$ ppm. Significant in pre-shift and post-shift urinary t,t-MA between smokers and non-smokers were found.

# PEOPLE AND DENGUE HAEMORRHAGIC FEVER PREVENTION PROGRAM IN RURAL NORTHEASTERN, THAILAND

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**Published in:** *Journal of Health Science* 2004;13:887-95.

**ABILITY,** enthusiasm, and responsibility of people are of important factors related to mechanism of disease prevention. The research aimed to study the people's participation with the dengue haemorrhagic fever (DHF) prevention program. This qualitative research was conducted in Ban Non, Muang District, Chaiyapum province with an indepth interview among 21 key informants who were village health volunteers, sub-district organization committee members, village committee, villagers, women group members, housewives and elderly. The method included observation of their DHF prevention activities in family and community levels. The results showed whether the people perceived themselves the disease threatened their family, the prevention activities such as mosquito breeding source eliminating, adult mosquito killing, and mosquito bite avoiding would be possible and sustainable. Collaboration with the local organizations and other public units for example, public health, school and local authority visibly decreased the number of incidence DHF cases. Because of this eager participation, the community became a healthy place.

# SHIGELLOSIS IN THE VIEW OF PATIENT AND PATIENT'S CARETAKER

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IN Thailand, there are many reported shigellosis cases in each year. It implied the presence of many factors related to persistence of the disease. This research conducted a qualitative study in 21 shigella cases and patients' caretakers (17 female and 4 male) who were living in rural and municipal areas of Kaeng Koi District, Saraburi Province. The information was collected by in-depth interview technique on patient and patient' s caretaker perceptions of symptoms and severity of shigellosis, as well as its cause, treatment, prevention, beliefs and health practices. The results showed that the respondents knew well about symptoms and causes leading to shigella infection and believed that shigellosis in children was more serious than in adults. Treatment pattern in children and adults usually started up from an observation of illness symptoms and then self-treatment, either drug medicine or herbs, to changed eating habits and lastly sought for health service at the near by health center.

**Published in:** *J Public Health* 2004; 34:29-38.

# SHIGELLOSIS IN THE VIEW OF COMMUNITY OF COMMUNITY LEADERS: A QUALITATIVE STUDY

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THERE are four main species of *Shigella*, S. *dysenteriae*, S. *Flexneri*, S. *boydii* and S. *sonnei*, which are able to cause diarrhea and/or dysentery. In Thailand, there are many reported shigellosis cases each year. It seems that various factors may have accommodated the continuing propagation of the disease. A qualitative study was conducted among 59 community leaders (health care providers, heads of community, women leaders and community teachers) who were living in rural and municipal areas in Kaeng Koi district, Saraburi province. The study focused on the community leaders, perceptions of symptoms, causes, serverity and risk groups of *Shigella*, as well as its treatment, prevention, beliefs and health practices. The information was collected by indepth interview technique. The study shows that the community leaders believed dysentery and diarrhea were not serious diseases because they could rely on self-medication, either modern and herbal medicine. However, they also currently had a prevention program such as food, drinking water and garbage disposal, especially in schools. Local views on about names, symptoms, causes, severity and risk groups of dysentery and diarrhea would be beneficial for upcoming health education, prevention, and treatment programs.

**Published in:** *Journal of Health Science* 2003;12:216-25.

# PHASE III TRIAL OF HIV PRIME-BOOST VACCINE COMBINATION IN THAILAND

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**BACKGROUND:** The world's first community-based, phase III HIV vaccine trial began in Thailand in late 2003. This is being carried out through the infrastructure of the Ministry of Public Health, augmented by Mahidol University and supported by the Armed Forces Research Institute of Medical Sciences.

**Objectives**: Determine if this prime-boost vaccine strategy 1) prevents infection, 2) alters disease course in vaccinees who become infected, and 3) is safe. Vaccines were designed specifically for the predominant circulating HIVs in Thailand (subtypes E and B). Prime: a recombinant canarypox ALVAC-HIV (vCP1521) with a subtype B gag/pro and gp41, and subtype E gp120 (R5) gene insertions (Aventis Pasteur). Boost: AIDSVAX" gp120 B/E, monomers of gp120 B (X4) + gp120 E (R5) with alum (VaxGen).

**Methods**: 16,000 HIV-negative adult Thais, screened and enrolled through the health care system of the Ministry of Public Health. Study design: randomized, placebo-controlled, double-blind phase III trial. Immunization is intramuscular over 6 months with a 3-year follow-up period.

**Results**: Clinical, laboratory and data system infrastructures have been built, qualified and validated; more than 400 staff trained, counseling and treatment networks strengthened, and communities engaged. HIV prevalence in volunteers assessed in a screening protocol was ~3%. During the initial 3-month phase-in period of the trial, more than 500 volunteers were enrolled.

**Conclusions**: With focus on a low-incidence, community-based population, the trial size is large, logistics very demanding and community engagement crucial.

**Oral Presentation**: The XV International AIDS Conference, 2004. Bangkok, Thailand. 11-16 July 2004.

# EPITOPE MAPPING OF MONOCLONAL ANTIBODIES SPECIFIC TO SEROVARS OF *LEPTOSPIRA*, USING PHAGE DISPLAY TECHNIQUE

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**RANDOM** heptapeptide library displayed by bacteriophage T7 was used to characterized epitopes of the monoclonal antibodies (mAb) clone F11, F20, F21, 2C3D4, and 8C6C4A12, which specific to serovar *L. australis*, *L. bratislava*, and *L. bangkok*, respectively. Phage selected by biopanning was cloned by plaque isolation, and the binding specificity of individual clones was confirmed by enzyme-linked immunosorbent assay, before further amplified and checked for phage peptide sequence using PCR and DNA sequencing. Interestingly, in phage reacting with the mAb clone F11, F20, 2C3D4, and 8C6C4A12, the deduced amino acid sequence of the displayed peptides was corresponded to a segment of hypothetical protein of *Leptospira* genome (*L. interrogans* serovar Lai and Copenhageni). Considering the deduced amino acid sequences of phage reacting with the mAb clone F11, F20, 2C3D4, and 8C6C4A12, the consensus motif -SKSSRC-, -TLINIF-, -SSKSYR- and -CTPKKSGRC- appeared respectively. No similarity was observed among phage reacting with the mAb clone F21. The results demonstrate that T7 phage display technique has potential for display of peptides and for rapid analysis of the interactions between these peptides with the mAb antibodies.

**Oral Presentation**: JITMM 2004, The Ambassador Hotel, Bangkok. 29 November - 1 December 2004.

# MUTATIONS IN THE *GYRA* AND *GYRB* GENES OF FLUOROQUINOLONE-RESISTANT *MYCOBACTERIUM TUBERCLUOSIS* FROM TB PATIENTS IN THAILAND

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◎ **AMONG** fluoroquinolone-resistant *Mycobacterium tuberculosis* (FQ-MTB) isolates, mutation at positions 90, 91, and 94 in *gyrA* gene and at positions 495, 516, and 533 in *gyrB* gene have been frequently reported. In this study, 35 isolates of FQ-MTB were collected from Siriraj Hospital and Chest Disease Institute. The quinolone resistance-determining regions (GRDR) of *gyrA* and *gyrB* genes in all 35 FQ-MTB isolates and from the H37Ra MTB strain were amplified using polymerase chain reaction (PCR). DNA-sequencing and single strand conformation polymorphism (SSCP) were further utilized for characterization of the mutations in the QRDR of *gyrA* and *gyrB* genes and mutation screening, respectively. From DNA-sequencing, 21 of 35 (60%) exhibited single-point mutations in different positions, at Ala90Val, Ser91Pro, and Asp94(Gly/Ala/His/Asn) and one novel mutation position at Gly88Cys in the *gyrA* gene and Asp495Asn in the *gyrB* gene. Moreover, one (2.9%) $FQ^r$-MTB strain found double mutation at Ala91Val and Asp94Asn. These positions were previously frequently reported to be responsible for $FQ^r$-MTB. The other 13 $FQ^r$-MTB isolates (37.1%) had no mutation. This study is the first report of mutation occurring only in the QRDR of the *gyrB* gene, without prior mutation in the QRDR of the *gyrA* gene, among $FQ^r$-MTB isolates. By SSCP analysis for screening of the mutant $FQ^r$-MTB, the SSCP patterns of mutated $FQ^r$-MTB isolates were clearly differentiated from the SSCP patterns of $FQ^s$-MTB.

**Oral Presentation**: JITMM 2004, The Ambassador Hotel, Bangkok. 29 November - 1 December 2004.

# EPITOPE MAPPING OF MONOCLONAL ANTIBODIES SPECIFIC TO *LEPTOSPIRA* SPP. USING PHAGE DISPLAY TECHNIQUE

**Pongrama Ramasoota[1], Rongdej Tungtrakarnpong[1], Patcharin saengjaruk[2], Gunna Froman[3], Wanpen Chaicumpa[4]**

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◎ **RANDOM** heptapeptide library displayed by bacteriophage T7 was used to characterize epitopes of the monoclonal antibodies clones LF9 and LD5 which are specific to all members of the genus *Leptospira*, and specific only to the pathogenic species, respectively. Bound phages were selected, followed by PCR and sequencing of inserted peptide sequences. Binding specificity of bound phages were confirmed by ELISA. In phage reacting with the LD5 monoclonal antibody, the deduced amino acid sequence of the displayed peptides corresponded to a segment of *Clostridium acetobutylicum* enome. Considering all the deduced amino acid sequences of phage reacting with the LD5 antibody, the consensus motif -DNY-PA- appeared. Considering all the deduced amino acid sequences of phage reacting with the LF9 antibody, the consensus motif -VLKKNTP- and -LXKNCS- appeared. No similarity was observed among phage reacting with the antibody clone LF9. The results demonstrate that T7 phage display technique has potential for display of peptides and for rapid analysis of the interactions between these peptides with monoclonal antibodies.

**Oral Presentation**: The TRF meeting new researcher meet senior researcher, Thailand. Research Fund 2004, 9-11 January 2004, Felix River Kwae, Kanjanaburi

# MUTATIONS IN THE *GyrA* AND *GyrB* GENES OF FLUOROQUINOLONE-RESISTANT *MYCOBACTERIUM TUBERCULOSIS* FROM TB PATIENTS IN THAILAND

**Pannamthip Pitaksajjakul[1], Waranya Wongwit[1], Wantanee Punprasit[2], Boonchuy Eampokalap[3], Sharon Peacock[4], Pongrama Ramasoota[1]**

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*Keywords: mutation, GyrA, GyrB, Fluoroquinolone-resistant,* Mycobacterium tuberculosis, *Thailand*

**AMONG** fluoroquinolone-resistant *Mycobacterium tuberculosis* (FQ$^r$-MTB) isolates, mutation at positions 90, 91, and 94 in *gyrA* gene and at positions 495, 516, and 533 in *gyrB* gene have been frequently reported. In this study, 35 isolates of FQ$^r$-MTB were collected from Siriraj Hospital and Chest Disease Institute. The quinolone resistance-determining regions (QRDR) of *gyrA* and *gyrB* genes in all 35 FQ$^r$-MTB isolates and from the H37Ra MTB strain were amplified using polymerase chain reaction (PCR). DNA-sequencing and single strand conformation polymorphism (SSCP) was further utilized for characterization of the mutations in the QRDR of *gyrA* and *gyrB* genes and mutation screening, respectively. From DNA-sequencing, 22 of 35 (62.9%) exhibited single-point mutations in different positions, at Ala90Val, Ser91Pro, and Asp94(Gly/Ala/His/Asn) and one novel mutation position at Gly88Cys in the *gyrA* gene and Asp495Asn in the *gyrB* gene. These positions were previously frequently reported to be responsible for FQ$^r$-MTB. The other 13 FQ$^r$-MTB isolates (37.1%) had no mutation. This study is the first report of mutation occurring only in the QRDR of the *gyrB* gene, without prior mutation in the QRDR of the *gyrA* gene, among FQ$^r$-MTB isolates. By SSCP analysis for screening of the mutant FQ$^r$-MTB, the SSCP patterns of mutated FQ$^r$-MTB isolates were clearly differentiated from the SSCP patterns of FQ$^s$-MTB.

**Oral Presentation**: The 4th National Symposium on Graduate Research August 10-11, 2004, Lotus Hotel Pang Siam Kaew, Chiang Mai.

# REDUCTION OF LOW BACK MUSCULAR DISCOMFORT THROUGH AN APPLIED ERGONOMICS INTERVENTION PROGRAM

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**AN** applied ergonomics intervention program (AEIP) was conducted with male employees working in the pressing and storage sections of a metal autoparts factory in eastern Thailand. The objective of this study was to reduce worker muscular discomfort at the low back. The study design was a participatory research approach with quasi-experimental pretest-posttest with a non-equivalent control group; 35 persons participated in the AEIP (AEIP group) and 17 persons did not (non-AEIP group). The AEIP was composed of 3 major categories: (1) top management support, (2) engineering designed some equipment for workstations and manual material handling, and (3) administrative intervention, training and health education. Muscle activities were measured by surface electromyography of the left and right erector spinae and multifidus muscles, and evaluated by multivariate test for dependent samples (paired observation), and for independent samples. After AEIP, the low back muscular loads of the AEIP group was significantly reduced while those of the non-AEIP group were not. Comparison of the means of %MVC of low back muscular activities between the AEIP group and non-AEIP group revealed that the AEIP group had significantly reduced low back muscular load with a 95% confidence level (P-value < 0.05).

**Poster Presentation**: JITMM 2004, The Ambassador Hotel, Bangkok 29 November – 1 December 2004.

# BRACKISH-WATER MOLLUSKS OF SURAT THANI PROVINCE, SOUTHERN THAILAND

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**BRACKISH-WATER** mollusks inhabiting the mangrove areas along the Gulf of Thailand of Surat Thani Province were investigated for distribution, abundance and natural infections. Nine families and thirty-two species of brackish-water snails were recovered from 14 sampling stations. *Cerithidea (Cerithideopsilla) cingylata*, *C. (C.) djadjariensis*, and *C. (Cerithidea) charbonnieri*, of the family Potamididae, were naturally infected with 2 types of cercariae, and one which was undetermined. *C. (C.) cingulata* had the highest infection rate (38.5%). Viewing two snail communities, the first community on the mainland and the second on Samui Island in Surat Thani Province, 28 brackish-water mollusk species were present on the mainland, 15 species were evident on Samui Island, and 11 snail species were common to both the mainland and Samui Island. Measurement of community similarity based on species presence revealed an index of similarity of 0.51. Concerning land use by the local people in the station areas investigated, brackish-water snails in Surat Thani Province are facing habitat degradation by human use.

**Poster Presentation**: JITMM 2004, The Ambassador Hotel, Bangkok 29 November – 1 December 2004.

# HEALTH PROMOTION PROGRAM FOR THE SAFE USE OF PESTICIDES IN THAI FARMERS

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**THE** purpose of this study was to determine the knowledge, attitude and practices (KAP) on safe use of pesticides of Thai farmers in Donka Subdistrict, Bangpae District, Ratchaburi Province. Thirty-three voluntary Thai farmers of thirty-three farmer families were recruited by convenience who praticipated in training program for six months. Data were collected by interviewed questionnaires and compared KAP on safe use of pesticides by paired t-test. Research finding showed that the mean scores of KAP in posttest were higher than pretest significantly. The results of this study provided health professionals with information to develop more effective prevention and intervention programs. To prevent illness, the most important role of health officers should focus on education and information for individuals, families and communities.

**Poster Presentation**: JITMM 2004, The Ambassador Hotel, Bangkok 29 November – 1 December 2004

# EMERGENCE OF *OPISTHORCHIS VIVERRINI* CERCARIAE FROM NATURALLY INFECTED *BITHYNIA* (*DIGONIOSTOMA*) *SIAMENSIS GONIOMPHALOS*

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**UNDER** natural conditions, the emergence of *Opisthorchis viverri* cercariae from naturally infected *Bithynia* (*Digoniostoma*) *siamensis goniomphalos* showed diurnal periodicity, peaking between 8-10 A.M. The cercaiae did not emerge during darkness, but low-intensity light could induce a release. Cercariae shedded from each field infected *B.(D.) s. goniomphalos* was recorded daily. The maximum output from one snail was 1,728 cercariae in a day. The total cercarial output from all five infected snails was 56,555 and the maximum of total cercariae shed from one snail was 27,692. The field-infected *B.(D.) s. goniomphalos* could survive for 70 days after the snails were collected.

**Poster Presentation**: JITMM 2004. The Ambassador Hotel, Bangkok. 29 November - 1 December 2004.

# SURVEILLANCE OF NON FATAL INJURY AND ACCIDENT AMONG CHILDREN UNDER FIVE YEARS OLD IN TAMBON AMPANG, AMPHOR BAN PAEW, SAMUT SAKHON PROVINCE, THAILAND

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**SURVEILLANCE** of non-fatal injury and accident among children under five years old was conducted in Tambon Ampang, Amphor Ban Paew, Samut Sakhon Province using questionnaires with face-to-face interview. Key informants were either parents or relatives or teachers who took care of the children. Data collection was conducted through a parent-teacher network of the Wat Sunthon-Satit Children Day Care Center. Preliminary study of injury/accident during the past 3 months among 15% sampling of a target population showed that 52% of the study samples were boys. Major cause of injury/accident accounted for was falls during walking and running (58%) followed by injury relating to toys (20%) and others (12%: burn, traffic, poison). Location of injury/accident occurred mostly in the outdoor setting (58%). This incidence accounted for 57% happened at day care center. Time at which injury/accident happened the most was during noon-afternoon (36%) followed by in the evening (31%), morning (21%) and at night (12%).

Data collected from this study on types, major causes, location and time of injury/accident among children under five years old in Samut Sakorn province can be used as baseline information for planning towards prevention and control in order to reduce childhood injury rates.

Oral Presentation, Tachin-Maeklong Integrated Research Project Meeting Mahidol University. December 28, 2004, The Royal James Hotel, Nakorn Pratom.

**Sources of funding**: Tachine-Maeklong Integrated Research Project towards Environmental Sustainability, Mahidol University, 2004.

# GENDER DIFFERENCE IN TREATMENT SEEKING BEHAVIORS OF TUBERCULOSIS CASES IN RURAL COMMUNITIES OF BANGLADESH

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**THIS** descriptive cross-sectional study was conducted to investigate gender differences in the epidemiological factors associated with the treatment seeking behaviors of TB cases in the rural communities of Bangladesh. The study reveals that there is significant gender difference in treatment seeking behaviors of rural TB cases and the majority of them (52%) have taken prior treatment from various traditional healers, 70% of them are females who attended health centers (UZHCs) as the other choice (adjusted OR: 4.2, 95% CI: 2.0-8.4). It was found that the mean patient delay was 63 days (range 14-210 days) where half of the females delayed more than 60 days while they were spreading their disease. The study findings reveal gender differences in treatment seeking behaviors associated with socio-cultural barriers, particularly among females in their access to TB care. Fifty-five percent of cases wanted the diagnosis of TB remain confidential to avoid being labeled as TB patients, where 82.7% were female, 85.6% of female TB patients had problems in their relationships with their spouse (61%) and family members (58%) after being diagnosed with TB. The results of the TB service factors found that 39% of females were not satisfied with their provider's behaviors, which was significantly associated with treatment seeking behavior (adjusted OR: 2.6, 95% CI: 1.0-6.6). The study findings strongly suggest that there was a significant gender difference in treatment seeking behavior in rural Bangladesh. Based on the study findings, we recommend developing an appropriate gender strategy for developing a TB control program, comprised of operational, socio-cultural and community awareness interventions aimed at treating undiscovered reservoirs of female TB cases in rural Bangladesh.

**Published in:** *Southeast Asian J Trop Med Public Health* 2004;35:126-35.

# PRIMARY VERIFICATION: IS THE TRISS APPROPRIATE FOR THAILAND?

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THE Trauma and Injury Severity Score (TRISS) is a well-accepted model used to evaluate the quality of trauma care in the US. This research aims to study whether TRISS can be applied to evaluate trauma care and classify outcomes of road traffic injury patients in Thailand. A retrospective study was used to review the Thailand's Injury Surveillance System database from the 1st January to the 31st of December 1996. The study subjects were severe road traffic injury patients with blunt injuries. The TRISS model was applied to compute the survival probability for each patient. The chi-square goodness-of-fit was used to compare the survival probability distribution between the American Major Trauma Outcome of Study (MTOS) and the road traffic injuries in Thailand. The accuracy, sensitivity and specificity of the survival prediction by TRISS were evaluated. The distribution of survival probability between American trauma patients and Thai road traffic injury patients was significantly different (p-value < 0.00001). The TRISS model had high accuracy and sensitivity, but low specificity, in predicting the survival of Thai road traffic injuries. The MTOS and Thai road traffic injuries had different distributions for various factors such as the Revised Trauma Score (RTS), Injury Severity Score (ISS), and ages which effect injury survival. Due to these factors the distribution of survival probability between MTOS and Thai road traffic injuries was also significantly different. By applying TRISS, the survival prediction of Thai road traffic injuries resulted in a high number of false positives.

**Published in:** *Southeast Asian J Trop Med Public Health* 2004 Mar; 35(1): 188-94.

# GENDER DIFFERENCES IN EPIDEMIOLOGICAL FACTORS ASSOCIATED WITH TREATMENT COMPLETION STATUS OF LEPROSY PATIENTS IN THE MOST HYPERENDEMIC DISTRICT OF NEPAL

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THE introduction of multidrug therapy(MDT), recommended by WHO, has been a major advance in the treatment of leprosy because of its relatively short treatment course and low rate of relapse. Although leprosy treatment is provided to both sexes equally, in most parts of the world significant differences have been found in treatment status. The main objective of the study was to investigate gender differences in epidemiological factors associated with treatment status of leprosy patients. An analytic cross-sectional study was carried out in the most hyperendemic Dhanusa District, Nepal. Stratified random sampling was applied for selection of the patients. Statistical analysis of the differences in treatment status, between males and females, and among other epidemiological factors of interest was carried out using multiple logistic regression. Chi-square/Fisher's exact test were also used to assess significances differences in values between males and females. There were 580 leprosy patients (385 male and 195 female) aged >15 years registered for MDT between April 1, 2001 to March 31, 2002 in the 16 main health centers of the district. Of the 580 patients, a total of 273 (183 male and 90 female) were included in the study, to collect data on clinical type of leprosy, patterns of physical deformity/disability, site of skin lesions, and socio-demographic information. There were183 male (68.3% on MB-MDT) and 90 female (61.1% MB-MDT) leprosy patients. We found that 79.2% of male patients completed treatment, while 34.4% female patients did not complete within the given time frame. Significant gender differences among leprosy patients were found in the distribution of disability grades and treatment completion status. However, there was no significant gender difference in the distribution of leprosy types and skin lesion sites. The study also found significant associations between treatment completion status and gender (adjusted OR 2.05, 95% CI: 1.07-3.94), education status (adjusted OR 2.37, 95% CI: 1.12-4.99), disability grade I (adjusted OR 3.14, 95% CI: 1.23-8.04), and disability grade 0 (adjusted OR 2.92, 95% CI: 1.14-7.47) after adjustment for all other leprosy/demographic factors.

**Published in:** *Southeast Asian J Trop Med Public Health* 2004 Dec; 35(2): 334-9.

# TEMPORAL TRENDS OF DENGUE FEVER/DENGUE HEMORHAGIC FEVER IN BANGKOK, THAILAND FROM 1981TO 2000: AN AGE-PERIOD-COHORT ANALYSIS.

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THE aim of this study was to examine the effects of age, time period, and birth cohorts with dengue fever/dengue hemorrhagic fever (DF/DHF) in Bangkok, Thailand over the period 1981-2000. The age group at greatest risk for DF/DHF was 5-9 years old. The period effect shows a remittent pattern, with significant increases in 1986-1990 and 1996-2000. The birth cohort group showed a significant decreasing trend from the 1961-1965 group to the 1991-1995 group ($R^2$ = 0.7620) with a decreasing rate of 0.1. We concluded that the temporal trend of DF/DHF is decreasing; especially for DHF.

**Published in:** *Southeast Asian J Trop Med Public Health* 2004 Dec; 35(4): 913-7.

# A PILOT FIELD TRIAL OF AN IN VITRO DRUG SUSCEPTIBILITY TEST USING THE ANAEROPACK, MALARIA CULTURE SYSTEM ON THE THAI-MYANMAR BORDER

**Hatabu T, Kawazu SI, Kojima S, Singhasivanon P, Krudsood S, Looareesuwan S, Kano S**

*Tropical Medicine and Health.*

THE AnaeoPack, malaria culture system with a portable thermostat incubator was evaluated in a field laboratory on the Thai-Myanmar border conducting in vitro drug susceptibility tests on blood samples from 5 Karen children infected with *P. falciparum*. Only one isolate was susceptible to chloroquine; the others were highly resistant. The $IC_{50}$ value of andisolate was only resistant to mefloquine, whereas the values of the 3 patients who presumably showed recrudescence were slightly elevated in the susceptible ranges. These results suggested that chloroquine should no longer be used for *P. falciparum* malaria in this geographic area, and that mefloquine should be carefully monitored for its *in vivo* effectiveness. In this study, the AnaeroPack, malaria culture system with portable thermostatic incubator is a powerful and useful mobile tool, which aids in providing detailed evidence based distribution data concerning of drug resistant malaria in the field.

**Published in:** *Tropical Medicine and Health* 2004;32(4):335-7.

# EVALUATION OF THE KAT-QUICK MALARIA RAPID TEST FOR RAPID DIAGNOSIS OF FALCIPARUM MALARIA IN THAILAND

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IN recent years, several rapid diagnostic tests for falciparum malaria have been developed. KAT test results were compared with microscopy on 90 consecutive patients hospitalized at the Hospital for Tropical Diseases, Bangkok, Thailand. Fifty-one patients had P. falciparum infections while 49 had malaria due to other plasmodium species. For a geometric mean +/-SD (Min;Max;range) parasitemia of 11,481 +/- 5.0 (88;713,838;713,750), the sensitivity of the KAT test was 96% (95% CI = 86-99.5), the specificity was 92% (95% CI = 80-99), the accuracy was 94% and the reliability was 85%. These findings suggest that the KAT test is of potential interest in the diagnosis of falciparum malaria in Thailand.

**Published in:** *Southeast Asian J Trop Med Public Health* 2004 Mar; 35(1): 35-7.

# OBESITY AND RELATED RESEARCHES IN THAIS

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วารสารราชบัณฑิตยสถาน (ฉบับเฉลิมพระเกียรติสมเด็จพระนางเจ้าสิริกิติ์ พระบรมราชินีนาถ ในโอกาสทรงเจริญพระชนมพรรษา 72 พรรษา 12 สิงหาคม 2547) ปี 2547 หน้า 424-433.

**OBESITY** researches and published papers in Thailand were reviewed according to the metabolism of overweight and obese subjects compared with normal subjects. The changes might cause important risks of chronic disease, such as hypertension, diabetes mellitus, carciovascular diseases, cancer etc. Molecular biological research into obesity is particularly interesting at the present time. Therefore, the results can be used in interventions for chronic diseases occurring in the overweight and obese.

# FOOD HABITS OF WOMEN WITH CERVICAL DYSPLASIA AND INVASIVE CERVICAL CANCER

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**A** comparative study was conducted with three female case groups (44 low cervical dysplasia, 70 high cervical dysplasia, and 43 invasive cervical cancer patients), and a control group of 95 women with normal cytological smear, using an 85-item Food Frequency Questionnaire to investigate the food habits of the studied groups. Information on demographic characteristics and other risk factors, sexual behavior, reproductive and menstrual history, exogenous hormone used, personal and familial medical history, and smoking habit, was also solicited. Polymerase chain reaction (PCR) was used to define the presence or absence of genital HPV DNA. The women with cervical dysplasia and invasive cervical cancer consumed various kinds of fruits and vegetables infrequently, and statistically less than the control group. This study indicated a relationship between nutritional habits and the risk of cervical cancer.

**Published in:** *J Nutr Assoc Thailand* 2004;39(1):p.22-34.

# FOLATE STATUS OF THAI WOMEN WITH CERVICAL DYSPLASIA

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**THE** study was carried out in Thai women that identified from the National Cancer Institute and Vajira Hospital in Bangkok, and Chonburi Cancer Center in Chonburi Province. Fasting blood samples were collected from 44 women with low-grade cervical neoplasia (CIN I), 70 high-grade cervical neoplasia (CIN II, III and carcinoma *in situ*) and 95 women with normal cytology as the control group for serum and red cell folate analysis and serum homocysteine determination. Cervical smears were obtained for histological diagnosis and colposcopy-directed biopsy investigation was used as confirmation. Polymerase chain reaction (PCR) was used to define the presence or absence of genital HPV DNA. The socioeconomic background, gynecologic history, and other possible risk factors were also gathered by personal interview and the daily intakes of folate were investigated by 24-hour recall, as well as the food habits of the subjects by food frequency questionnaire. The low folate statuses of these women showed a strong association with cervical dysplasia. The serum folate was markedly lower than the control group in both low-grade ($p<0.01$) and high-grade cervical neoplasia cases ($p<0.01$). Moreover, using logistic regression, the Odds ratio for low-

grade cervical neoplasia with low serum folate level (<19.82 nmol/L) was 6.13, while that of the high-grade group with the same folate level was 5.57. The investigation of the relationship between abnormality of the cervical cells and red cell folate and serum homocysteine produced similar results. The outcome of folate intake analysis and the food habits of these women were related to the folate status of the blood. This finding supported the contention that the folate deficiency status of the women in this study increased the risk of cervical change.

Financial Supported by Mahidol University

**Abstract in:** APJCN 2004;13: Supplement S171.

## ULTILIZATION OF NUTRIENT SOURCES BY FEMALE *ANOPHELES DIRUS* (DIPTERA: CULICIDAE)

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IN this study, we studied the utilization of blood and sugar as nutrient sources by female *Aopheles dirus* when they were fed blood on day 2 and day 5 after emergence. When female *An. dirus* fed blood on day 2 after emergence, the levels of glycogen and sugar significantly increased. Beside that, the increase in glycogen was affected by sucrose feeding. An increase in lipid with time after blood feeding was not observed. However, Mosquitoes fed only blood had significantly more lipids than that those fed blood plus sucrose solutions. On the other hand, the amount of glycogen and lipid and sugar did not significant increase when female *An. dirus* fed blood on day 5 after emergence. It is concluded that there is energetic advantage to *An. dirus* when they feed on blood early in adult life before on day 2 after emergence as well as the study in *Aedes agepti*.

**Presented in:** Joint International Tropical Medicine Meeting 2004, 29 November -1 December 2004, Ambassador Hotel, Bangkok, Thailand.

## CHROMOSOME 10 AND 17 DELETIONS AND P53 GENE MUTATIONS IN THAI PATIENTS WITH ASTROCYTOMAS

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THE tumor suppressor gene locus is known to be partly responsible for the tumorigenesis of sporadic gliomas, but the genetic events that drive the neoplastic process of this tumor remain largely unknown. We correlated the results of loss of heterozygosity (LOH) analysis on chromosomes 10 and 17 and a point mutation analysis of a tumor suppressor gene, p53, in 21 patients with astrocytomas at different stages. LOH was determined in tumor and leukocyte DNAs of primary human central nervous system tumors. The incidence rate of brain tumors corresponded to every p53-coding exon for single-strand conformation polymorphisms (SSCP) and the mutations were confirmed by sequencing. p53 mutations were found in 2 of 10 glioblastomas (20%) and in 1 of 8 low - grade astrocytomas (12.5%). Similarly, LOH on chromosome 10 was also found in 2 of 10 glioblastomas (20%) and 1 of 8 low - grade astocytomas (12.5%). Neither of the p53 mutations nor LOH on chromosome 10 was observed together in the tumor types analyzed. Interestingly, the p53 mutations were found in 29% of patients with LOH on chromosome 17. The fact that p53 mutation and LOH on chromosome 17 were found blastomas together only in glioblastomas, suggested that these genetic changes may accumulate during astrocytoma progression.

Oncology Report 2004;11:207-211.

# IDENTIFICATION OF DNA AMPLIFICATION IN CHROMOSOME 6Q23-24 IN BREAST CANCER

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This study was supported by National Center for Genetic Engineering and Biotechnology (BIOTECH), Thailand.
**Presented in:** The fifth Princess Chulabhorn International Science Congress, Evolving Genetics and its Global Impact, August 16-20, 2004; p. 34, Thailand

**BREAST** cancer is the most common cancer among women worldwide. In Thailand, breast cancer is the second among all site of cancer in female. This report, the genetic alterations in breast cancer from Thai patients were analyzed by arbitrarily primed polymerase chain reaction (AP-PCR). DNA extracted from 30 breast tissues and corresponding normal tissues were amplified with 60 random primers. The DNA fingerprinting obtained from each primer were detected by agarose gel electrophoresis compared between cancer and normal. 18 out of 30 cases exhibited a gene amplification in DNA fingerprinting amplified from primer D15. The nucleotide sequence of this amplified fragment was determined by DNA sequencing and identifed using Blastn programme. Result reveled that this amplified fragment was located in chromosome 6q23-24. This amplified fragment was significantly associated with the increasing of tumor site (P = 0.02, Odds ratio = 11.25), indicated that the DNA amplification in chromosome 6q23-24 may involved in the progression of breast tumor.

# IDENTIFICATION OF NOVEL GLUTATHIONE-S-TRANSFERASE GENE ALTERATIONS IN OVARIAN CANCER

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Financial supported by: Faculty of Tropical Medicine, Mahidol University
**Presented in:** The Fifth Princess Chulabhorn International Science Congress, Evolving Genetics and its Global Impact, August 16-20, 2004; p. 34, Thailand

**OVARIAN** cancer is the third most common gyanecological malignancy in Thailand. The molecular basis of ovarian cancer development is not yet clear. This study, the genetic alterations in ovarian cancer was carried by arbitrarily primed polymerase chain reaction (AP-PCR) and nucleotide sequencing. The amplified fragment in IVS-4 of novel glutathione-S-transferase class omega 2 (GSTO2) gene located on chromosome 10q24-25 was identified. The gene mutations in all 6 exons of GSTO2 were determined by single strand conformation polymorphism (SSCP) and DNA sequencing. The A to C transition at codon 142 in exon 4 (AAT to GAT, Asn142Asp) was identified. This base change was also observed in normal individual leukocyte DNA and was assigned as a gene polymorphism. Therefore, the frequency of GSTO2 gene polymorphism was analysed in ovarian cancer, breast cancer and normal individual by PCR-RFLP. The frequency of GSTO2 polymorphism was 77.3%, 36.6% and 36.6% in ovarian cancer, breast cancer and normal women individual, respectively. Statistical analysis indicated that A/G polymorphism in GSTO2 codon 142 was significantly associated with the risk of ovarian cancer (P=0.015, Odds ratio=3.33).

# GENE AMPLIFICATION ON CHROMOSOME 4P15.2 IN BREAST CANCER

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This work was supported by the National Center for Genetic Engineering and Biotechnology and the National Cancer Institute (BIOTECH) Bangkok, Thailand Second Regional APOCP Conference – South East Asia, 9-11th February, 2004, Khon Kaen University, Thailand

**GENE** amplification is clearly demonstrated as a promising aspect of tumor growth and development and has prognostic importance in certain cancers. From our previous study, genetic alterations in Thai patients with breast cancer were analyzed by random amplified polymorphic DNA with sixty arbitrary primers, showing that primer D15 detected gene gains at the highest frequency (80%). The amplified DNA fragment was then isolated and identified as approximately 600 bp sequences mapped to chromosome 4p15.2 and 6q23-24, respectively. The specific primers on chromosome 4p15.2 were further designed and used to detect gene amplification in paraffin-embedded tissues of patients with breast cancer by real time PCR. Our results indicated that the gene amplification was detected in 9 out of 23 cases (39%). More cases have been performed to evluate the prognostic value. However, our present findings suggest that amplification of the gene located on chromosome 4 is involved in the tumorigenesis of breast cancer in Thai patients.

# ATHEROSCLEROSIS AND CIVILIZATION

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The Journal of Thammasat University Medical School 2004;5(1):55-64.

**CIVILIZATION,** industrialization, urbanization, economic development and market globalization cause rapid change in human diets and lifestyle. This is having significant impact on health and nutritional status of population. While standard of living have improved and more foods are available, there have been significant negative consequence on overconsume high-fat and energy dense foods, decrease physical activity, increase tobacco use and corresponding increase diet-related chronic disease as obesity, high blood pressure, diabetes mellitus and the most seriously, coronary heart disease, that is the number 1 killer of adult world population. Primary strategy for the prevention of cardiovascular disease should include reducing cardiovascular risk factors, change unhealthy lifestyle choices by recommending dietary modifications, smoking cessation, and exercise regimens.

# REDUCED MICROCIRCULATORY FLOW IN SEVERE FALCIPARUM MALARIA: PATHOPHYSIOLOGY AND ELECTRON-MICROSCOPIC PATHOLOGY

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**THE** pathophysiology of severe falciparum malaria is complex, but evidence is mounting that its central feature is the old concept of a mechanical microcirculatory obstruction. Autopsy studies, but also *in vivo* observations of the microcirculation, demonstrate inhomogeneous distributed obstruction of the microcirculation in severe malaria. The principal cause for this is cytoadherence to the vascular endothelium of erythrocytes containing the mature forms of the parasite, leading to sequestration and obstruction of small vessels. Besides, parasitized red cells become rigid, compromising their flow through capillaries whose lumen has been reduced by sequestered erythrocytes. Adhesive forces between infected red cells (auto-agglutination), between infected and uninfected red cells (rosetting) and between uninfected erythrocytes

(aggregation) could further slow down microcirculatory flow. A more recent finding is that uninfected erythrocytes can also become rigid in severe malaria. Reduction in the overall red cell deformability has a strong predictive value for a fatal outcome. Rigidity is presumably caused by oxidative damage to the red blood cell membrane by malaria pigment released at the moment of schizont rupture. Anti-oxidants like N-acetylcysteine can reverse this effect and are promising as adjunctive treatment in severe malaria.

**Published in:** *Acta Tropica* 2004;89: 309-17.

## CRYPTOCOCCAL MENINGITIS IN HUMAN IMMUNODEFICIENCY VIRUS (HIV)-POSITIIVE AND HIV-NEGATIVE PATIENTS

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**THIS** study compared clinical manifestations, blood biochemistry and cerebrospinal fluid (CSF) results of HIV-positive and HIV-negative patients with cryptococcal meningitis. We collected 57 cases of cryptococcal meningitis from cytological specimens submitted to the Department of Tropical Pathology, Faculty of Tropical Medicine. Pertinent clinical data were analysed retrospectively in 47 cases for clinical manifestations, laboratory features and outcomes of 38 HIV-positive and 9 HIV-negative patients. Headache was the most common symptom seen in all cases, of which 70.2 % occurred with fever. CSF examination of both groups revealed elevated opening pressure. Increased CSF protein and depressed CSF glucose levels were seen in HIV-negative cases, which differed from HIV-positive cases, where a slight change was noted. CSF pleocytosis in HIV-positive patients was varible. Forty-eight percent of HIV-positive patients had CSF leukocyte counts below 20 cells $mm^3$. None was found in the HIV-negative patients. Specific treatments with amphotericin B and fluconazole were given. Five fatal cases of cryptococcal meningitis were noted, all of which were HIV-positive. There were statistically significant differences in blood neutrophils, blood eosinophils, CSF leukocyte counts, CSF neutrophils CSF lymphocytes, CSF glucose, and CSF total protein, in HIV-positive and HIV-negative patients (p=0.050, p=0.022, p=0.002, p=0.016, p=0.047, p=0.031, respectively).

**Published in:** *Southeast Asian J Trop Med Public Health* 2004;35 (Suppl 1):1-6.

## COMPARISON OF CRYPTOSPORIDIUM PARVUM DEVELOPMENT IN VARIOUS CELL LINES FOR SCREENING *IN VITRO* DRUG TESTING

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**THIS** study describes the development of *Cryptosporidium parvum* in MDCK, MA-104, Hep-2 and Vero cell lines. Differences in susceptibility, infectivity, and the methodology of excystation were determined. Various solutions were considered to determine the factors which enhanced the excystation (*eg* with and without sodium hypochlorite, trypsin or sodium taurocholate). It was shown that the sporozoites could be excysted in media either with or without trypsin and sodium taurocholate, but the number of sporozoites in the latter solution was less than the former one. Only oocysts digested by sodium hypochlorite and trypsin can enter the culture cells. Numerous meronts and oocysts were demonstrated and persisted for 9 days. Asexual stages were not observed in MA-104. Only few oocysts could be detected 1-3 days post-inoculation. There was a significant difference between the number of oocysts, which invaded MDCK, MA-104, and Hep-2 cells. MDCK gave the highest susceptibility to oocyst

invasion among the three cell lines and asexual stages were also found. Among the 25 isolates, which had been cultivated, 23 isolates could infect MDCK and Hep-2. Only 2 isolates could not infect the MDCK cell. These 2 isolates could infect the Vero cell and yielded high numbers of trophozoites. Praziquantel (PZQ), doxycycline, and paromomycin (PRM) were tested on the infecting parasites. The drugs were added either with the inoculum or 24 hours after inoculation. None of them was effective, including PRM, which had been previously reported as effective.

**Published in:** *Southeast Asian J Trop Med Public Health* 2004;35(3):540-6.

## DEVELOPMENT OF ISOSPORA BELLI IN HCT-8, HEP-2, HUMAN FIBROBLAST, BEK AND VERO CULTURE CELLS

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**THE** development of *Isospora belli*, a human coccidian parasite, was studied in different cell lines. Merozoites were observed in all kinds of cells, whereas sporogony was demonstrated only in Hct-8. This implied that not only the human cell line can be infected, but also some animal cell lines. Unizoites could be found in Vero cells. The merozoites were transferred to a new culture cell for three passages and maintained for two weeks, but no oocyst production was observed in any culture cells during cultivation.

**Published in:** *Southeast Asian J Trop Med Public Health* 2004;35(4):796-800.

## PATHOLOGICAL INVESTIGATION OF RED CELL DEFORMATION IN SEVERE MALARIA

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**THE** pathogenesis of severe malaria involves the sequestration of malaria-infected red blood cells in the deep vessels of key organs such as the brain, kidney and lung. Whilst there has been extensive research into the role of receptor mediated adhesion between infected red blood cells (iRBC) to host endothelial cells, the role of non-receptor mediated adhesion of both iRBC and uninfected red blood cells (uRBC) is less well understood. These events may play a key role in retarding, but not completely obstructing, blood flow in tissues during severe malaria. Evidence from *in vitro* and *in vivo* experiments supports the theory that there are changes to the red cell membrane structure in both iRBC and also uRBC during malaria infection, and that these profoundly effect the rheological characteristics of red cell flow and deformability during severe malaria. We will present pathological data gained from light and electron microscopic examination of fatal malaria cases in 60 adult South East Asian patients, which examined the pathological features of severe malaria in multiple organs including the brain and kidney. Ultrastructual and quantitative histological data will be presented which demonstrates that uRBC are increased in the brain during cerebral malaria, as well as sequestration of iRBC. In addition changes in red cell structure and membrane fluidity occur, which may contribute to vascular sequestration, reduced blood flow and transient hypoxia. We will discuss these findings in the light of the pathological changes in the kidney and brain in severe malaria, and also in contrast to other diseases, such as sickle cell anaemia and sepsis, where changes in red cell membrane deformability contribute to pathology.

**Oral Presentation:** Joint International Tropical Medicine Meeting, 29 November- 2 December 2004. Ambassador Hotel, Bangkok Thailand

# DEVELOPMENT OF INTRACELLULAR PROTOZOA BY TISSUE CULTURE ON COVER GLASSES AND DETECTION BY STAINING METHODS

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**Oral Presentation**: Journal of Microscopy Society of Thailand 2004, 21st The Microscopy Society of Thailand February 25-27, 2004 Ubon-Ratchathani, Thailand, 18(1):40.

**THE** aim of the study was to develop in vitro culture of *Isospora belli*, *Cryptosporidium parvum* and *Microsporidium spp*. From human feces which are intracellular protozoa for medical importance. The development of these parasities in various cell lines were observed by both fresh preparations and staining methods. Iron haematoxylin-eosin, Giemsa, modified acid fast and Gram chromotrope were also used, according to the stages of the parasites. Merozoites or asexual stage was stained by either Iron haematoxylin-eosin or Giemsa where as oocysts or sexual stage was stained by modified acid fast and Iron haematoxylin-eosin. Spores of *Microsporidium* from culture were stained by Gram chromotrope as reported for stool specimens. The extra cellular stages of *Cryptosporidium parvum* could not be stained by all these staining methods which had been described above. The morphology of these protozoa were determined and discussed and compared with the paraffin-embedded tissue section. Cover glass staining was clearly demonstrated the development of protozoa in tissue culture.

# VASCULAR MODEL FOR STUDYING NITRIC OXIDE RELATED ANTI-ATHEROSCLEROTIC AGENTS; PRELIMINARY STUDY

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**Oral Presentation**: The 21st Microscopy Society of Thailand, February 25-27, 2004 Ubon-Ratchathani, Thailand
**Published in**: *Journal of Microscopy Society of Thailand* 2004;18(1):41

**DYSFUNCTION** of endothelial cell (EC) to produce endothelial nitric oxide synthase (eNOS) is one of major etiologies of atherosclerosis. Consequently pathologic changes related to atherosclerosis include increase in platelet aggregation and adhesion to EC, elevated adhesion molecules on EC enhanced inflammatory cells binding to EC and proliferation of smooth muscle cell. Therefore, NO related antiatherogenic agents are one drug of choices to improve or protect atherosclerosis. Presently, no *in vitro* model for studying the efficiency of these drugs is available. In our study, *in vitro* EC model was constructed using human umbilical vein endothelial cells (HUVEC) grown in 6.5 mm in diameter transwell and cocultures with SMC in 24 well plate to mimic the character of artery. To incubate HUVEC confluent monolayer with TNF- a (10 ng/ml) for 12 hours, prior to exposure to 17b –estradiol (100 pg/ml) for 12 hours were used to cause EC defection, and recovery in eNOS production, respectively. The ultrastructure of HUVECs in the model of atherosclerosis were determined and evaluated the possibility of the model by scanning and transmission electron microscope. In conclusion, we propose this model can basically be conducted for early study to investigate the safety, clinincal activity, and pharmacokinetic profile of NO related anti-atherosclerotic agents.

# HUMAN LACTOFERRIN IN THE BRAIN TISSUE OF FATAL FALCIPARUM MALARIA

**Yaowapa Maneerat, Dennis Shanks, Parnpen Viriyavejakul, Benjanee Punpoowong, Vasant Khachansaksumeth, Pacheun Potup, Sornchai Looareesuwan**

**LACTOFERRIN (LF),** an iron-binding glycoprotein, exist in milk, other body fluids, serum, and specific granules of neutrophils. Previous studies suggested that LF inhibited the invasion of *Plasmodium falciparum* (*P. falciparum*) sporozoite into host hepatocyte. The role of LF in inhibition of cytoadherence by its binding to several endothelial receptors is still not understood clearly. To prove the inhibitory effect of LF on cytoadherence, we determined the correlation between the severity of histopathologic changes and the distribution of LF in formalin fixed paraffin embedded brain tissue sections of 10 cerebral, 10 noncerebral malaria patients and 5 normal controls. LF in each brain tissues was localized by immunoperoxidase technique using rabbit polyclonal antibody to human LF. The most prominent histopathologic changes in cerebral malaria section included edema, neuronal degeneration, ring haemorrhage and sequestration of *P. falciparum* infected red cells in vessels. LF positive staining was found obviously only in cytoplasm of neutrophils intravasculatures and around ring haemorrhage but not at the surface of endothelial cells in vessels. The distribution of LF in other parts of brain tissues was rare and not significantly different among both patient groups and control. Contrastly, strong LF staining endothelial cells were found in one brain smear from a cerebral malaria patient. In conclusion, inhibitory effect of LF on cytoadherence in brain tissues of fatal malaria was controversial. Further studies to localize LF in endothelial cell coculturing with *P. falciparum* infected red cells will be needed to better understanding.

**Poster Presentation:** The 12th International Congress of Immunology and 4th annual Conference of FOCIS, 18-23 July, 2004, Montreal, Canada

# CD23 EXPRESSION, *PLASMODIUM FALCIPARUM* SPECIFIC IGE AND TUMOR NECROSIS FACTOR-ALPHA PRODUCTION IN THAI FALCIPARUM MALARIA PATIENTS

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**THE** present study was designed to determined if there was any correlation between on one hand CD23 expression on monocytes, total and *P. falciparum* specific IgE, as well as TNF- levels and on the other malaria severity. The number of patients enrolled in this study was 65 with uncomplicated, 24 with severe, 150 with uncomplicated but with concomitant helminthic infections and 66 with severe malaria and with helminthic infections but free of malaria parasites, 30 healthy donors served as controls. CD23 expressed on monocytes was quantified by flow cytometry. Levels of soluble CD23 (sCD23), total and *P. falciparum* specific IgE and TNF- were determined by enzyme-linked immunosorbent assay (ELISA). The median expression of CD23 on monocytes in severe patients was significantly higher than that seen in uncomplicated patients ($p = 0.004$). CD23 expression was followed from admission and up to one month after admission. The highest levels were seen on day 2 in the severe malaria patients both with and without helminthic infections. The plasma sCD23 levels in the severe patients were slightly higher although not statistically significant when compared to the other patient groups and in the controls. The median of *P. falciparum* specific IgE (787.8 pg/ml) was higher in the severe malaria groups than in the other groups and controls while the median of total IgE did not differ between the groups. The medians of *P. falciparum* specific IgG (25 ug/ml) and of TNF- (6.5 ng/ml) was higher in the uncomplicated

patients than in the other patient groups and controls. The levels of TNF- were maximal on day 7 in the severe malaria but without (6.43 ng/ml) with helminthic infection (5.9 ng/ml). A significant positive correlation ($r$ = 0.205, $p$ = 0.035) between *P. falciparum* specific IgE and TNF- was seen. There was no correlation between the density of CD23 expression and severity of disease. Taken together our data revealed that there was no obvious correlation between CD23 expression, *P. falciparum* specific IgE levels and TNF- and the severity of disease. Moreover, there was no difference in disease severity between the patients with and without helminthic coinfection.

**Poster Presentation**: The 12th International Congress of Immunology and 4th Annual Conference of FOCIS, 18-23 July, 2004, Montreal, Canada

## THE MODIFICATION OF HEMATOXYLIN STAINING METHOD FOR *PLASMODIUM SPP* IN HUMAN PERIPHERAL BLOOD SMEAR

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**MALARIAL** disease remains one of the major public health problems in the tropical and subtropical countries. Nowadays, the microscopic diagnosis of this disease is essential; human peripheral blood smear is stained with Wright staining or Field staining and examined under light microscope for the detection of the parasite. Although the treatment continuously has been improved; however, For the best result of treatment, malarial count in the blood smear is always used during the period of treatment. In all others forms of malaria, the diagnosis is confirmed by the demonstration of nuclei and cytoplasm in red blood cell in a smear. The organism are best revealed by Wright's stain, the nuclei appear as red round or red ovoid structures and the cytoplasm was bluish-violet in the reddish-violet red blood cell. The identification of the blood stages of closely allied species of parasites presents unusual difficulties, because the morphology and behavior of the organisms are easily affected by minute changes of technique. The most satisfactory procedure is to compare the blood smears under identical condition, i.e. at the same time, in similar stages of the infection in a host of the same age and species and stained by precisely similar methods, indicating the brand of strain, and the diluents. Malarial parasite in blood smears can be stained with a variety of dyes. Some of the stains consist of a complex mixture of refine methylene blue and eosin that result the nuclei of the organism appear as red round while the cytoplasm was bluish-violet in the reddish-violet red blood cell. In some cases, there were few malarial parasite in the blood smear and the color of the reddish-violet red blood cell interferes the identification. We modified hematoxylin staining method for the staining of *Plasmodium* spp in human peripheral blood smear. In this modification method, the parasite took on a bluish stain while the red blood cell was colorless.

**Poster Presentation**: Joint International Tropical Medicine Meeting, 29 November- 2 December 2004. Ambassador Hotel, Bangkok Thailand

## ULTRASTRUCTURAL CHANGES OF PANCREATIC ISLETS MICROCIRCULATION IN NONOBESE DIABETIC (NOD) MICE

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**INSULIN-DEPENDENT** diabetes mellitus (IDDM) or human type I diabetes, in most cases, is caused by autoimmune destruction of the insulin-producing beta cells within the pancreatic islets of Langerhans. The mononuclear cells infiltrate in the islets which results in the development of insulitis, a prerequisite step for the development of diabetes, are primarily composed of T cells. T cells play an important roles in initiating and propagating an autoimmune process in destroying beta cells. In patients, IDDM is a chronic disease that may involve with other vascular disorders such as hypertension and atherosclerosis. The objective of this study was to investigate the ultrastructural changes

of pancreatic islets microcirculation using transmission electron microscopic technique. The obstacles of the study in human have been replaced in the nonobese diabetic (NOD) mice. NOD mice is genetically predisposed for the spontaneous development of type I diabetes. Many genetic and immunologic features of diabetes in NOD mice are shared with those in the human diabetes. NOD mice homozygous for the severe combined immune deficiency spontaneous mutation (*Prkdc*$^{scid}$, referred as SCID) do not have autoimmune diabetes since they lack T and B cells due to the SCID mutation. So, NOD mice is an animal mode for human type I diabetes and NOD/LtSz-*Prkdc*$^{scid}$ mice is as a control strain. The major ultrastructural changes of pancreatic islets microcirculation in NOD mice is notified by vascular endothelial cell swelling. Some insulin-producing beta cells were destroyed but some cells are in normal structure with insulin-secretory granules. There is no change of the pancreatic acinar cell. These changes indicate the relationship between diabetes and changes of pancreatic islets microcirculation in NOD mice and may related to the changes in human microcirculation of type I diabetes and other related human vascular disorder.

**Oral presentation**: Joint International Tropical Medicine Meeting 2004, Ambassador Hotel, Bangkok, Thailand, 29 November-1 December 2004.

# A QUANTITATIVE ULTRASTRUCTURAL STUDY OF THE LIVER AND THE SPLEEN IN FATAL FALCIPARUM MALARIA

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WE performed a retrospective study of 25 patients who died of severe falciparum malaria in Thailand and Vietnam using electron microscopy. The aims of the present study were: to determine if there was any significant association between parasitized red blood cell (PRBC) sequestered in liver or spleen and particular pre-mortem clinical complications and to compare the degree of parasite load between the liver and spleen within the same patients. PRBC sequestration in the spleen was higher than the liver (S.I. median = 3.13, 0.87, respectively) ($p<0.05$). The results of quantitative ultrastructural study of the present study showed a significantly higher parasite load in the liver of patients with jaundice, hepatomegaly and liver enzyme elevation ($p<0.05$). We found a significant correlation between PRBC sequestration in the liver and the level of serum bilirubin, the level of aspartate aminotransferase (AST) and the size of palpable liver (Spearman's correlation coefficient = 0.688, 0.572, 0.736, respectively). Furthermore, more parasite load was found in the liver of patients with acute renal failure (ARF) compared to patients without ARF ($p<0.05$). These findings suggest that PRBC sequestration in the liver is quantitatively associated with pre-mortem hepatic dysfunction and renal impairment. There was no significant difference between splenomegaly and PRBC sequestration and the size of palpable spleen was not correlated to parasite load in the spleen. When ultrastructural features were compared between tow reticuloendothelial organs, we found that the spleen had more PRBC and phagocytes than the liver and the spleen of non-cerebral malaria (NCM) patients had more phagocytes than cerebral malaria (CM) patients. This observation provided that the spleen plays a major role in the malaria parasites clearance and associated with host defence mechanism against malaria.

# PHARMACOKINETIC INVESTIGATION OF ALBENDAZOLE AND PRAZIQUANTEL IN THAI CHILDREN INFECTED WITH *GIARDIA INTESTINALIS*

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**THE** pharmacokinetics of albendazole/albendazole sulphoxide and praziquantel were investigated in Thai children with *Giardia* infection. Twenty school-aged children were randomly allocated to receive either a single oral dose of albendazole (400 mg/child) or the same dose of albendazole given concurrently with a single oral dose of praziquantel (20mg/kg). The concentrations of albendazole/albendazole sulphoxide and praziquantel in plasma samples, collected at intervals in the first 24 h post-treatment, were then quantified using HPLC with ultra-violet detection. No significant pharmacokinetic interaction between the albendazole and praziquantel was demonstrated. For albendazole suphoxide, the active metabolite of albendazole, there was marked inter-individual variation in the maximum plasma concentration and the " area under the curve". The pharmacokinetics of albendazole sulphoxide were similar whether albendazole was given alone or in combination with praziquantel.

**Published in:** *Ann Trop Med Parasitol* 2004;98(4):349-57.
(Funding by Department of Tropical Pediatrics, Faculty of Tropical Medicine, Mahidol University)

# IMMUNOGENICITY AND SAFETY OF PRE-EXPOSURE IM AND ID REGIMENS OF PURIFIED CHICK EMBRYO CELL RABIES VACCINE ADMINISTERED CONCOMITANTLY WITH JAPANESE ENCEPHALITIS VACCINE IN TODDLERS

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**Presented at:** 2nd Asian Congress of Pediatric Infectious Diseases in conjunction with 26th Annual Congress of The Malaysian Paediatric Association, September 2-4, 2004, Sutera Harbour resort, Kota Kinabalu, Malaysia.
(Funding by Chiron Vaccines, Germany)

**AIMS:** To compare the immunogenicity and safety of Purified Chick Embryo Cell rabies vaccine (PCECV) for primary pre-exposure prophylaxis after intramuscular (IM) and intradermal (ID) injections given concomitantly with Japanese encephalitis vaccine (JEV) in toddlers.

**Methods:** The subjects, 200 healthy toddlers aged 12 to 18 months were randomized 2:2:2:2:1 to receive one of four pre-exposure PCECV regimens administered within one month: 1 ml IM x 3, 0.5 ml IM x 3, 0.1 ml ID x 3, 0.1 ml ID x 2. These four groups also received JEV x 2. The 5th group received JEV x 2 only. Safety was evaluated after each injection. Pre- and post-vaccination blood samples were analyzed for neutralizing antibodies to rabies and Japanese encephalitis virus (JE).

**Results:** At day 49 after the first injection, all PCECV recipients seroconverted against rabies (RFFIT antibody titers $\geq$ 0.5 IU/ml) and JE (JE antibody titers $\geq$ 10 serum dilution). Both vaccines were well tolerated.

**Conclusions:** The concomitant administration of PCECV (IM or ID) and JEV in toddlers is safe and induces protective antibodies against both rabies and JE.

# CLINICAL MANIFESTATIONS OF UNCOMPLICATED FALCIPARUM MALARIA AND VIVAX MALARIA IN THAI CHILDREN

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**BACKGROUND:** Differentiation between malignant malaria (caused by *P. falciparum*) and non-malignant malaria (caused by *P. vivax*) is important in clinical management of malaria. The clinical manifestations of uncomplicated malaria may help in species identification and early management to prevent its complication.

**Objectives:** To compare clinical manifestations of uncomplicated falciparum and vivax malaria.

**Methods:** One hundred and seventy admission records of pediatric patients with uncomplicated falciparum and vivax malaria admitted to the Hospital for Tropical Diseases or Thongpaphum Hospital, from 1991 to 2003, were reviewed. The demographic data, clinical manifestations and treatment outcomes were analyzed.

**Results:** Seventy-seven patients had vivax malaria, 90 falciparum malaria and 3 mixed infections. Weakness and dehydration were significantly higher in falciparum malaria, but chills were more common in vivax malaria. White blood cell, eosinophil, basophil, lymphocyte, abnormal lymphocyte counts and serum sodium levels in falciparum malaria were significantly lower than vivax malaria. Vivax malarial patients received the standard chloroquine regimen. The mean fever clearance time (FCT) was 36.7 hours and the mean parasite clearance time (PCT) was 58.6 hours. The cure rate was 100%. Fifty-four falciparum malarial cases received oral quinine for 8 days. The mean FCT and PCT were 66 and 68 hours, respectively. The cure rate was 75.4%. The remaining falciparum malarial patients were treated with rectal artesunate followed by mefloquine. The mean FCT and PCT were 39 and 50 hours, respectively. The cure rate was 91.6%.

**Conclusions:** Even though some clinical manifestations were helpful for differentiating the causes of uncomplicated malaria, they were not specific. Thus blood smears were still necessary for diagnosis. Chloroquine was still effective for vivax malaria.

**Presented at:** The 12th ASEAN Pediatric Federation Conference " Impact of Child Care on Adult Diseases" & The 58th Thai Congress of Pediatrics, November 26-28, 2004, Dusit Resort Hotel, Pattaya, Thailand.
(Funding by Department of Tropical Pediatrics, Faculty of Tropical Medicine, Mahidol University)

# RECTAL ARTESUNATE FOR COMPLICATED FALCIPARUM MALARIA IN CHILDREN

**Krisana Pengsaa[1], Chukiat Sirivichayakul[1], Kesara Na-Bangchang[2], Itthipon Thaiarporn[3], Anong Chaivisuth[4], Amnaj Wongsuwan[5], Pataraporn Wisetsing[1], Phanorsri Attanath[1], Pornthep Chanthavanich[1], Arunee Sabchareon[1]**

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**BACKGROUND:** In areas of multidrug resistance, artesunate rectal suppository has been suggested by the World Health Organization for severe/complicated falciparum malaria in adult and pediatric patients at the community health care level prior to transfer.

**Objective:** To study the effectiveness of artesunate rectal suppository in complicated childhood falciparum malaria.

**Methods:** Thirteen children from the Thai-Myanmar border, with severe/complicated falciparum malaria were randomly allocated: group 1 (5 cases) received rectal artesunate 20 mg/kg followed by 10 mg/kg at $H_{12}$ and $H_{24}$; Group 2 (8 cases) received rectal artesunate 10 mg/kg at $H_0$, $H_4$, $H_{12}$ and $H_{24}$. Both groups then received rectal artesunate 10 mg/kg/d x 3 days. Mefloquine 25 mg/kg was given orally at $H_{72}$ in a split dose 6 hr later. Thick and thin blood smears were performed in all cases at 6 – hr interval x 2 after treatment then at 12-hr interval until malarial- parasite negative 2

times, then at $D_7$, $D_{14}$ and $D_{28}$. Parasite clearance time and fever clearance time were used for the outcome criteria.

**Results:** All the patients recovered uneventfully, including 3 cases of cerebral malaria who gained consciousness within 20 hr after treatment. The median 90% parasite reduction times were 12 and 11 hr, and the median fever clearance times were 44 and 62 hr in groups 1 and 2, respectively. No adverse effects from the drugs, and no recrudescence after the follow-up period of 28 days, were observed in all cases.

**Conclusions:** Intrarectal artesunate was effective, well tolerated and can be life-saving drug in severe/complicated multidrug-resistant falciparum malaria in children.

**Presented at:** The 12th ASEAN Pediatric Federation Conference " Impact of Child Care on Adult Diseases" & The 58th Thai Congress of Pediatrics, November 26-28, 2004, Dusit Resort Hotel, Pattaya, Thailand.
(Funding by Department of Tropical Pediatrics, Faculty of Tropical Medicine, Mahidol University)

# EARLY ANTIBODY RESPONSE TO MULTIPLE DOSES OF INTRAMUSCULAR, PURIFIED VERO CELL RABIES VACCINE

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**RABIES** is still a major public health problem in many parts of the world. One of the causes of treatment failure is the relatively long lag between rabies vaccinations and the resultant active protective antibody response. The early antibody response is important when passive prophylaxis with rabies immunoglobulin is not available. To find rabies vaccination regimens that might induce rapid antibody response, we studied antibody response to multiple doses intramuscular (IM) purified Vero cell rabies vaccine (PVRV) on days (D) 0 and 3. One hundred and twenty healthy adult volunteers with no history of previous rabies immunization were randomly assigned to one of the 3 IM PVRV regimens: Group A (n = 40) received 2-site injections on D0, 3 and then 1-site on D7, 14 and 28; Group B (n = 40) received 3-site injections on D0 (bilateral injections at the deltoid and a single injection at the lateral thigh) and then 1-site on D3, 7, 14 and 28; Group C (n = 40) received 1-site injections on D0, 3, 7, 14 and 28 (standard regimen). Neutralizing antibody (NAb) determinations were performed on D0, 5, 7, 14, 28 and 365 using the rapid fluorescent focus inhibition test at Queen Saovabha Memorial Institute, Bangkok, Thailand. The ages, weights, heights and genders were similar among the 3 groups. Nine subjects were excluded from antibody analysis since they had detectable rabies NAb on D0 (cut-off point of rabies NAb 0.07 IU/ml). On D5, two subjects (5.4%) in Group A had NAb 0.15 IU/ml. On D7, more subjects in Group A (30%), and Group B (26%) had NAb 0.15 IU/ml than Group C (11%); however, they were not significantly different. Seroconversions (NAb 0.5 IU/ml) on D7 were detected in 5.4% and 5.3% of groups A and B, respectively, but none in Group C. On D14 and 28, all of the subjects in the 3 groups seroconverted. At one year, the seroconversion of groups A, B and C were 65%, 92% and 75%, respectively. The geometric mean titers of the 3 groups were similar on D7, 14, 28 and 365. Side effects of the three regimens were in the acceptable range, without significant difference. Comparing side effects according to the number of injections showed that more than one injection per day had significantly more myalgia, asthenia, headache, dyspnea and urticaria.

In conclusion, multiple IM doses on D0 and 3 (groups A and B) insufficiently induced early antibody response; therefore rabies immunoglobulin is still indispensable in category III rabies exposure. Multiple IM doses also had no impact on long-term protection.

**Presented at:** Joint International Tropical Medicine Meeting 2004, November 29 – December 1, 2004, Ambassador Hotel, Bangkok, Thailand.
(Funding by Aventis Pasteur (Thailand) Co., Ltd.)

# HAEMATOLOGICAL STATUS, PLASMA VITAMIN B12 AND FOLIC ACID LEVELS, AND INTESTINE PATHOLOGY IN RATS INFECTED WITH *GIARDIA LAMBLIA*

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**THE** purpose of our study was to investigate the haematological status, vitamin $B_{12}$ and folic acid absorption and intestinal pathology after *Giardia lamblia* infection in a rat model. Adult Wistar rats were assigned randomly to receive human giardia cysts orally in the amount of $5 \times 10^5$ or $1.0 \times 10^6$ cysts, or none in the controls. The results showed that all rats injected with giardia cysts become infected. The cysts output in the infected rats varied considerably. In rats infected with $5.0 \times 10^5$ giardia cysts, the incubation period until cyst output was 10 days compared with 4 days in rats infected with the higher amount of $1.0 \times 10^6$ giardia cysts. The highest peaks for cysts output in these 2 groups were on day 4 - 33 which decreased gradually to day 40 - 58. The hematocrit and hemoglobin levels in the infected rats were statistically significantly lower than in the controls on day 16, 22, 33, and 37 post-infection ($p < 0.05$). A reverse relationship between giardia cysts output and hemoglobin concentration was found in the infected rats ($p = 0.05$). There were no significant differences in plasma vitamin $B_{12}$ and folic acid levels between the infected rats and the control rats. No pathological changes were found in the small intestine of infected rats. These findings suggested that giardiasis did not affect the absorption of plasma vitamin $B_{12}$ and folic acid but caused anemia in a rat model.

**Published in:** *Southeast Asian J Trop Med Public Health* 2004;35(4):811-6.

# ACETYLCHOLINESTERASE AND CHOLINESTERASE ACTIVITIES IN *GIARDIA LAMBLIA* TROPHOZOITES CULTURED *IN VITRO*

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**AXENIC** culture of *Giardia lamblia* trophozites *in vitro* was conducted from patients infected with *Giardia lamblia*. The cholinesterase (ChE) and acetylcholinesterase (AChE) activities were determined in cultured Giardia trophozoites. The enzyme activities were found in boh tissue-bound and tissue-free forms. There was low ChE and AChE enzyme activities in trophozoites (1.6095 ± 1.0981; 0.9626 ± 0.1322; 0.1387 ± 0.0783; 0.0752 ± 0.0877 Units/mg protein, respectively). The tissue-bound and tissue-free ChE enzymes were found in a greater amount than tissue-bound and tissue-free AChE enzymes. The presence of these enzymes in Giardia may involved in the motility of Giardia trophozoites.

# ACETYLCHOLINESTERASE AND CHOLINESTERASE ACTIVITIES IN RATS INFECTED WITH *GIARDIA LAMBLIA*

**Cheeraratana Cheeramakara[1], Apichat Nontprasert[2], Wanyarat Thanomsak[1], Kriyaporn Songmuaeng[1], Nophachai Suthisai[1], Bangorn Sukchut[1], Suvit Areekul[1]**

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**Presented at:** Joint international Tropical Medicine Meeting 2004, Bangkok, Thailand. 29 November – 1 December 2004.

**THIRTY-THREE** adult Wistar rats were assigned randomly to receive either 1.0 x $10^6$ human *Giardia lamblia* cysts (n = 18) or controls (n = 15). Actylcholinesterase (AChE) and cholinesterase (ChE) activities in the infected rats were compared with the controls. The results showed that the plasma ChE activities in the infected rats were statistically significant higher than controls on day 10, 25, 29, 33, and 40 post-infection and decreased to baseline after day 49 post-infection. The red cell AChE activities in the infected rats were higher than the controls on day 37, 55, and 58 post-infection. There was a reverse correlation between Giardia cysts output and red cell AChE activity in the infected rats. This study suggested that there was no liver involvement but enhancement of erythropoiesis secondary to anemia in rats infected with *Giardia lamblia*.

# INFLUENCE OF SMOKING ON TOTAL HOMOCYSTEINE, FOLATE, VITAMIN $B_2$, $B_6$, $B_{12}$ AND VITAMIN C CONCENTRATIONS IN HEALTHY THAI MALES

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**Presented at:** Joint international Tropical Medicine Meeting 2004, Bangkok Thailand. 29 November – 1 December 2004

**CIGARETTE** smoking and elevated plasma total homcysteine are considered to be the increased morbidity and mortality risk of cardiovascular diseases. B vitamins regulate the metabolism of homocysteine via remethylation and transsulfuration pathways. The purpose of this study was to investigate the effects of cigarette smoking on the blood status of various B vitamins, vitamin C and total homocysteine concentrations in healthy Thai male smokers and nonsmokers. This cross-sectional study was carried out among smokers and nonsmokers from suburban and urban residential areas in Bangkok, Thailand. The 187 smokers and 101 nonsmokers (19-62 years) who participated voluntarily in the study, were investigated. Total homocysteine, folate, vitamin $B_2$, $B_6$, $B_{12}$ and C concentrations were measured. Total homocysteine concentration in plasma was significantly higher among smokers compared to nonsmokers. Serum vitamin $B_{12}$ and C concentrations were significantly lower among smokers compared to nonsmokers. Furthermore, the folate concentration in smokers was lower than that of nonsmokers, but it was not statistically significant. Vitamin $B_2$ and $B_6$ displayed insufficient vitamin status among 52.9% and 20.9% of the smokers, respectively. These findings suggest that smoking cause an increased plasma total homocysteine concentrations. The decreased vitamin status might be due to different dietary intake patterns as well as increased utilization of many vitamins among smokers.

# RANDOMIZED, CONTROLLED DOSE-OPTIMIZATION STUDIES OF DIHYDROARTEMISININ-PIPERAQUINE FOR THE TREATMENT OF UNCOMPLICATED MULTIDRUG-RESISTANT FALCIPARUM MALARIA IN THAILAND

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**BACKGROUND.** Dihydroartemisinin-piperaquine (DP) is a new and relatively inexpensive artemisinin-containing fixed-combination antimalarial treatment. An adult treatment course contained 6.4 mg/kg dihydroartemisinin (DHA), which is >40% lower than the level in most artemisinin-containing combinations. This raised the possibility that the efficacy of the current coformulation may not be optimal in the treatment of multidrug-resistant falciparum malaria.

*Methods.* In 2 large randomized, controlled studies in Thailand, the recommended dose of DP was compared with a regimen with additional artemisinin derivative (12 mg/kg; DP+) and with mefloquine plus artesunate (MAS3).

*Results.* A total of 731 patients were included: 201 in a hospital-based study and 530 in a community study. Day-28 cure rates in the hospital-based study were 100% (95% confidence interval [CI], 93.9%-100%) in the MAS3 and DP+ groups and 98.3% (95% CI, 91%-99.7%) in the DP group, with a single recrudescence on day 21. In the community study, polymerase chain reaction genotyping-adjusted cure rates on day 63 were 96.1% (95% CI, 92.6%-99.7%) in the DP group, 98.3% (95% CI, 96.1%-100%) in the DP+ group, and 94.9% (95% CI, 91.2%98.6%) in the MAS3 group ($P$ = .2). Adverse events were few, with an excess of mild abdominal pain in the DP group.

*Conclusions.* The current dosage of DP (6.4 mg/kg DHA and 51.2 mg/kg piperaquine phosphate) given over the course of 48 h is highly effective, safe, and well tolerated for the treatment of multidrug-resistant falciparum malaria, and its efficacy is not improved by the addition of more DHA.

Wellcome Trust-Mahidol University-Oxford Tropical Medicine Research Programme funded by the Wellcome Trust of Great Britain.
**Published in:** *The Journal of Infectious Diseases* 2004;190:1773-1782.

# FIELD EVALUATION OF A NOVEL COLORIMETRIC METHOD-DOUBLE-SITE ENZYME-LINKED LACTATE DEHYDROGENASE IMMUNODETECTION ASSAY-TO DETERMINE DRUG SUSCEPTIBILITIES OF PLASMODIUM FALCIPARUM CLINICAL ISOLATES FROM NORTHWESTERN THAILAND

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**A** double-site enzyme-linked lactate dehydrogenase enzyme immunodetection assay was tested against field isolates of *Plasmodium falciparum* for assessing in vitro drug susceptibilities to a wide range of antimalarial drugs. Its sensitivity allowed the use of parasite densities as low as 200 parasites/µl of blood. Being a nonisotopic, colorimetric assay, it lies within the capabilities of a modest laboratory at the district level.

Wellcome Trust-Mahidol University-Oxford Tropical Medicine Research Programme funded by the Wellcome Trust of Great Britain.
**Published in** *Antimicrobial Agents and Chemotherapy* 2004;48:1426-9.

# COMBINATION ANTIFUNGAL THERAPIES FOR HIV-ASSOCIATE CRYPTOCOCCAL MENINGITIS: A RANDOMISED TRIAL

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**BACKGROUND:** It frequently takes more than 2 weeks for drug treatments for cryptococcal meningitis to sterilise cerebrospinal fluid (CSF). In-vitro and animal studies lend support to the use of combinations of amphotericin B, flucytosine, and fluconazole for treatment of cryptococcosis. We compared the fungicidal activity of combinations of these drugs for initial treatment of patients with cryptococcal meningitis.

*Methods*: 64 patients with a first episode of HIV-associated cryptococcal meningitis were randomised to initial treatment with: amphotericin B (0.7 mg/kg daily); amphotericin B plus flucytosine (100 mg/kg daily); amphotericin B plus fluconazole (400 mg daily); or triple therapy with amphotericin B, flucytosine, and fluconazole. Our primary endpoint was fungicidal activity, measured by the rate of reduction in CSF cryptococcal colony-forming units (CFU) from serial quantitative CSF cultures on days 3, 7, and 14 of treatment.

*Findings*: Baseline CSF CFU counts were an important prognostic factor. Clearance of cryptococci from the CSF was exponential and was significantly faster with amphotericin B plus flucytosine than with amphotericin B alone (p=0.0006), amphotericin B plus fluconazole ( p=0.02), or triple therapy (p=0.02).

*Interpretation*: At these doses, amphotericin B plus flucytosine is the most rapidly fungicidal regimen. Quantification of CSF cultures provides a powerful new means to accurately assess the fungicidal activity of new treatment regimens for cryptococcal meningitis

Wellcome Trust-Mahidol University-Oxford Tropical Medicine Research Programme funded by the Wellcome Trust of Great Britain.
**Published in:** *Lancet* 2004;363:1764-7.

# DIFFERENTIAL EXPRESSION OF INTERFERON (IFN)-Y AND IFN-Y-INDUCING CYTOKINES IN THAI PATIENTS WITH SCRUB TYPHUS OR LEPTOSPIROSIS

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**INTERFERON** (IFN)- plays an important role in the induction of a type 1 immune response against intracellular pathogens. We compared the plasma levels of IFN- and IFN—inducing cytokines in adult Thai patients with scrub typhus, cause by the obligate intracellular bacterium *Orientia tsutsugamushi*, and leptospirosis, cause by extracellular *Leptospira interrogans*. IFN-, interleukin (IL)-18, and IL-15 levels were elevated only in patients with scrub typhus, whereas IL-12p40 and tumor necrosis factor- concentrations were elevated in both patient groups, although more so in scrub typhus. These data suggest a role for a cell-mediated immune response in host defense against *O. tsutsugamushi*.

Wellcome Trust-Mahidol University-Oxford Tropical Medicine Research Programme funded by the Wellcome Trust of Great Britain.
**Published in:** *Clinical Immunology*, 2004;113:140-4.

# THE CHANGING PATTERN OF BLOODSTREAM INFECTIONS ASSOCIATED WITH THE RISE IN HIV PREVALENCE ON NORTHEASTERN THAILAND

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A survey of bloodstream infections was conducted in the large regional hospital in Ubon Ratchatani, northeastern Thailand between 1989 and 1998, during the onset of the HIV epidemic. The incidence of *Staphylococcus aureus*, *Escherichia coli*, *Klebsiella/Enterobacter* and *Pseudomonas aeruginosa* bacteraemias remained constant whereas infections caused by *Burkholderia pseudomallei*, non-typhoid *Salmonellae*, *Cryptococcus neoformans*, *Penicillum marneffei* and to a lesser extent *Streptococcus pneumoniae* all rose. *Burkholderia pseudomallei* infections were unrelated to HIV, whereas the other infections were associated directly with HIV. Group D non-typhoid *Salmonellae* bloodstream infections (mainly *Salmonella enteritidis*) rose coincident with the increase in HIV seroprevalence, and preceded the increase in the other HIV-associated infections. Other non-typhoid *Salmonella* bacteraemias increased two years after the rise in group D infections, and invasive yeast infections increased four years later, coincident with the increase in AIDS. Increasing Group D non-typhoid *Salmonella* bloodstream infections are an early warning signal of an impending rise in AIDS.

Wellcome Trust-Mahidol University-Oxford Tropical Medicine Research Programme funded by the Wellcome Trust of Great Britain.
**Published in**: *Transactions of the Royal Society of Tropical Medicine and Hygiene* 2004;98:678-86.

# IN VITRO EFFICACY OF ANTIMALARIAL DRUGS AGAINST *PLASMODIUM VIVAX* ON THE WESTERN BORDER OF THAILAND

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THE susceptibility of 20 isolates of *Plasmodium vivax* on the Thailand-Myanmar border to seven antimalarial drugs was evaluated using the schizont maturation inhibition technique. The geometric mean 50% inhibition concentration (IC50) values were quinine = 308 ng/mL, amodiaquine =14 ng/mL, chloroquine =50 ng/mL, mefloquine = 127 ng/mL, sulfadoxine/pyrimethamine (80:1) = 800/10 ng/mL, pyrimethamine = 8 ng/mL, and artesunate = 0.5 ng/mL. Compared with *P. falciparum* in this area, *P. vivax* was more sensitive to chloroquine and artesunate, equally sensitive to quinine, and more resistant to mefloquine.

Wellcome Trust-Mahidol University-Oxford Tropical Medicine Research Programme funded by the Wellcome Trust of Great Britain.
**Published in**: *The American Journal of Tropical Medicine and Hygiene* 2004;70:395-7.

# PLATELET-INDUCED AUTOAGGLUTINATION OF *PLASMODIUM FALCIPARUM* INFECTED RED BLOOD CELLS AND DISEASE SEVERITY IN THAILAND

**Kesinee Chotivanich,[1] Juntima Sritabal,[1] Rachanee Udomsangpetch,[2] Paul Newton,[1,4] Katarzyna A Stepniewska,[1,4] Ronatrai Ruangveerayuth,[3] Sornchai Looareesuwan,[1] David J Roberts,[5] Nicholas J White[1,4]**

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**THE** relationship of the platelet-mediated autoagglutination of *Plasmodium falciparum*-infected red blood cells (IRBCs) to disease severity was investigated in 182 Thai patients with falciparum malaria; it was evident in 43% of uncomplicated malaria ($n$ = 63), 41% of severe malaria ($n$ = 104), and 100% of cerebral malaria ($n$ = 15; $P$ = .001) isolates. The median (range) number of IRBCs in agglutinates per 1000 IRBCs was significantly higher in cerebral malaria (6 [3-42]) than in severe (0 [0-52]) and uncomplicated (0 [0-24]) malaria ($P$ = .01). In multivariate analyses, high parasitemia and cerebral malaria were associated independently with parasite agglutination.

Wellcome Trust-Mahidol University-Oxford Tropical Medicine Research Programme funded by the Wellcome Trust of Great Britain.
**Published in:** *The Journal of Infectious Diseases* 2004;189:1052-5.

# ARTESUNATE-DAPSONE-PROGUANIL TREATMENT OF FALCIPARUM MALARIA: GENOTYPIC DETERMINANTS OF THERAPEUTIC RESPONSE

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**THE** combination of chlorproguanil and dapsone is being considered as an alternative antimalarial to sulfadoxine–pyrimethamine in Africa, because of its greater efficacy against resistant parasites, and its shorter half-lives, which exert less selective pressure for the emergence of resistance. A triple artesunate–chlorproguanil–dapsone combination is under development. In a previous study of relatively low-dose chlorproguanil–dapsone in multidrug-resistant falciparum malaria in Thailand failure rates were high. Proguanil is inexpensive, widely available and very similar to chlorproguanil. The safety and efficacy of artesunate–dapsone–proguanil (artesunate 4 mg/kg, dapsone 2.5 mg/kg, proguanil 8 mg/kg daily for three days), was studied prospectively in 48 Thai adult patients with acute falciparum malaria followed daily for 28 days. Eleven of these had a recrudescence of their infection. Genotyping of *Plasmodium falciparum* dihydrofolate reductase (*dhfr*) and dihydropteroate synthase (*dhps*) indicated that the *Pfdhfr* I164L mutation was the main determinant of therapeutic outcome; all 11 failures carried this mutation (failure rate 11/37; 30%) whereas none of the 11 infections with 'wild type' 164 genotypes failed. The addition of artesunate considerably augments the antimalarial activity of the biguanide–dapsone combination, but this is insufficient for infections with parasites carrying the highly antifol-resistant *Pfdhfr* I164L mutation.

Wellcome Trust-Mahidol University-Oxford Tropical Medicine Research Programme funded by the Wellcome Trust of Great Britain.
**Published in:** *Transactions of the Royal Society of Tropical Medicine and Hygiene* 2004;99:142-9.

# THE EFFECTS OF *PLASMODIUM FALCIPARUM* AND *PLASMODIUM VIVAX* INFECTIONS ON PLACENTAL HISTOPATHOLOGY IN AN AREA OF LOW MALARIA TRANSMISSION

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**PLACENTAL** histopathology was studied in a cohort of 204 women living in an area of low *Plasmodium falciparum* and *P. vivax* malaria transmission. Detection of malaria antenatally was active, by weekly peripheral blood smears, and all infections were treated. Significant histopathologic placental malaria changes (increased malaria pigment, cytotrophoblastic prominence, and presence of parasites) were found only in a minority of women who had *P. falciparum* infections in pregnancy. These changes were significantly more frequent in women with evidence of peripheral blood infection close to delivery and only in these cases were placental inflammatory cells increased. Antenatal *P. vivax* infection was associated only with the presence of malaria pigment in the placenta. All placental infections diagnosed by blood smear and 32.4% (12 of 37) diagnosed by histopathology were associated with patent peripheral parasitemia. This study indicates that prompt treatment of peripheral parasitemias during pregnancy limits placental pathology. The effect on birth weight reduction may not result from irreversible placental changes but from the acute insult of infection. These findings emphasize the importance of treating malaria in pregnancy promptly with effective antimalarial drugs

Wellcome Trust-Mahidol University-Oxford Tropical Medicine Research Programme funded by the Wellcome Trust of Great Britain.
**Published in:** *American Journal of Tropical Medicine and Hygiene* 2004; 70:398-407.

# A SYSTEMATIC OVERVIEW OF PUBLISHED ANTIMALARIAL DRUG TRIALS

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**SYSTEMATIC** database searches identified 435 antimalarial drug treatment trials, involving 82 616 patients, conducted and published between 1966 and December 2002. Of these trials 72% were randomised; 64 (15%) trials involved severe malaria, 47 (11%) studied *Plasmodium vivax*, 3 *Plasmodium malariae* or *Plasmodium ovale*, and the remainder (74%) assessed treatment responses in uncomplicated falciparum malaria. Twelve trials (2.7%) specifically evaluated antimalarial treatments in pregnant women. Overall 49% of trials were conducted in Asia (29% from Thailand alone) and 42% in Africa. Half of all the patients studied had been in trials published in the past 7 years. There has been a recent rise in the proportion of trial enrolling children, and a tripling in the average number of patients recruited per trial (from approximately 100 in the 1970s to 300 currently). Chloroquine was given to over half the patients in antimalarial drug trials ($n$=53552) compared with artemisinin derivatives ($n$=12463), mefloquine-sulphadoxine-pyrimethamine ($n$=9153), mefloquine ($n$=5546) and sulphadoxine-pyrimethamine ($n$=5909). The quality of safety and efficacy data for recently evaluated drugs contrasts with a relative paucity of data for older 'established' compounds.

Wellcome Trust-Mahidol University-Oxford Tropical Medicine Research Programme funded by the Wellcome Trust of Great Britain.
**Published in:** *Transactions of the Royal Society of Tropical Medicine and hygiene* 2004;98:73-81.

# MEFLOQUINE RESISTANCE IN PLASMODIUM FALCIPARUM RESULTS FROM INCREASED PFMDR1 GENE COPY NUMBER

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**BACKGROUND:** The borders of Thailand harbour the world's most multidrug resistant *Plasmodium falciparum* parasites. In 1984 mefloquine was introduced as treatment for uncomplicated falciparum malaria, but substantial resistance developed within 6 years. A combination of artesunate with mefloquine now cures more than 95% of acute infections. For both treatment regimens, the underlying mechanisms of resistance are not known.

**Methods:** The relation between polymorphisms in the *P. falciparum* multidrug resistant gene 1 (*pfmdr1*) and the in-vitro and in-vivo responses to mefloquine were assessed in 618 samples from patients with falciparum malaria studied prospectively over 12 years. *pfmdr1* copy number was assessed by a robust real-time PCR assay. Single nucleotide polymorphisms of *pfmdr1*, *P falciparum* chloroquine resistance transporter gene (*pfcrt*) and *P. falciparum* Ca2+ ATPase gene (*pfATP6*) were assessed by PCR-restriction fragment length polymorphism.

**Findings:** Increased copy number of *pfmdr1* was the most important determinant of in-vitro and in-vivo resistance to mefloquine, and also to reduced artesunate sensitivity in vitro. In a Cox regression model with control for known confounders, increased *pfmdr1* copy number was associated with an attributable hazard ratio (AHR) for treatment failure of 6·3 (95% CI 2·9-13·8, p<0·001) after mefloquine monotherapy and 5·4 (2·0-14·6, p=0·001) after artesunate-mefloquine therapy. Single nucleotide polymorphisms in *pfmdr1* were associated with increased mefloquine susceptibility in vitro, but not in vivo.

**Interpretation:** Amplification in *pfmdr1* is the main cause of resistance to mefloquine in falciparum malaria.

**Relevance to practice:** Multidrug resistant *P. falciparum* malaria is common in southeast Asia, but difficult to identify and treat. Genes that encode parasite transport proteins maybe involved in export of drugs and so cause resistance. In this study we show that increase in copy number of *pfmdr1*, a gene encoding a parasite transport protein, is the best overall predictor of treatment failure with mefloquine. Increase in *pfmdr1* copy number predicts failure even after chemotherapy with the highly effective combination of mefloquine and 3 days' artesunate. Monitoring of *pfmdr1* copy number will be useful in epidemiological surveys of drug resistance in *P. falciparum*, and potentially for predicting treatment failure in individual patients.

Wellcome Trust-Mahidol University-Oxford Tropical Medicine Research Programme funded by the Wellcome Trust of Great Britain.
**Published in:** *Lancet* 2004;364: 438-47.

# ACTIVITIES OF ARTESUNATE AND PRIMAQUINE AGAINST ASEXUAL- AND SEXUAL-STAGE PARASITES IN FALCIPARUM MALARIA

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**THE** activities of primaquine in combination with quinine or artesunate against asexual- and sexual-stage parasites were assessed in 176 adult Thai patients with uncomplicated *Plasmodium falciparum* malaria. Patients were randomized to one of the six following 7-day oral treatment regimens: (i) quinine alone, (ii) quinine with tetracycline, (iii) quinine with primaquine at 15 mg/day, (iv) quinine with primaquine at 30 mg/day, (v) artesunate alone, or (vi) artesunate with primaquine. Clinical recovery occurred in all patients. There were no significant differences in fever clearance times, rates of *P. falciparum* reappearance, or recurrent vivax malaria between the six treatment groups. Patients treated

with artesunate alone or in combination with primaquine had significantly shorter parasite clearance times (mean +/- standard deviation = 65 +/- 18 versus 79 +/- 21 h) and lower gametocyte carriage rates (40 versus 62.7%) than those treated with quinine (P < or = 0.007). Primaquine did not affect the therapeutic response (P > 0.2). Gametocytemia was detected in 98 patients (56% [22% before treatment and 34% after treatment]). Artesunate reduced the appearance of gametocytemia (relative risk [95% confidence interval] = 0.34 [0.17 to 0.70]), whereas combinations containing primaquine resulted in shorter gametocyte clearance times (medians of 66 versus 271 h for quinine groups and 73 versus 137 h for artesunate groups; P < or = 0.038). These results suggest that artesunate predominantly inhibits gametocyte development whereas primaquine accelerates gametocyte clearance in *P. falciparum* malaria.

Wellcome Trust-Mahidol University-Oxford Tropical Medicine Research Programme funded by the Wellcome Trust of Great Britain.
**Published in:** *Antimicrobial Agents and Chemotherapy* 2004;48:1329-34.

## THERAPEUTIC RESPONSES TO ANTIMALARIAL AND ANTIBACTERIAL DRUGS IN VIVAX MALARIA

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◎ ***PLASMODIUM VIVAX*** is the most prevalent malaria infection and is an important cause of morbidity in Central and South America and Asia. *P. vivax* is generally sensitive to the common antimalarial drugs but high level resistance to chloroquine and/or pyrimethamine has been documented in some geographic locations. In the studies reviewed here, the therapeutic responses to antimalarial and antibacterial drugs in vivax malaria have been assessed in the Bangkok Hospital for Tropical Diseases. The evaluated drugs consisted of the eight most widely used antimalarial drugs and anti-bacterial drugs that possess antimalarial activities (tetracycline, doxycycline, clindamycin or azithromycin). The activities of these drugs in descending order of parasite clearance times were artesunate, artemether, chloroquine, mefloquine, quinine, halofantrine, primaquine, followed by the antibacterial drugs and lastly sulfadoxine-pyrimethamine. Clinical responses to sulfadoxine-pyrimethamine were also poor with evidence of high grade resistance in 42% of the patients. Of the four antibacterial drugs, clindamycin was more effective than azithromycin and can be an alternative to the tetracyclines. Except for chloroquine and mefloquine which have long plasma half lives and may therefore suppress first relapses, the cumulative cure rates for the short acting antimalarial drugs were similar. Double infection with *Plasmodium falciparum* was common and usually manifested 3-4 weeks following clearance of vivax malaria. The prevalence of cryptic falciparum malaria was 8-15% and was higher in patients treated with less potent antimalarial drugs. Follow-up studies have revealed that the relapse time in Thai patients with vivax malaria is on average only 3 weeks, but can be suppressed by the slowly eliminated antimalarial drugs such as chloroquine and mefloquine. For accurate comparison of relapse/recrudescence rates in vivax malaria, at least 2 month's follow-up is required. It can be concluded that in malarious areas of Thailand, double infection with *P. falciparum* and *P. vivax* is common affecting at least 25% of the patients and usually manifests as sequential illnesses. *P. vivax* in Thailand is sensitive to chloroquine but has acquired high grade resistance to sulfadoxine-pyrimethamine.

Wellcome Trust-Mahidol University-Oxford Tropical Medicine Research Programme funded by the Wellcome Trust of Great Britain.
**Published in:** *Acta Tropica* 2004; 89:351-6.

# IN VIVO ASSESMENT OF DRUG EFFICACY AGAINST *PLASMODIUM FALCIPARUM* MALARIA: DURATION OF FOLLOW-UP

**Kasia Stepniewska[1,2], Walter RJ Taylor[3], Mayfong Mayxay[4], Ric Price[1,2], Frank Smithuis[5], Jean-Paul Guthmann[6], Karen Barnes[7], Hla Yin Myint[1], Martin Adjuik[3], Piero Olliaro[3], Sasithon Pukrittayakamee[1], Sornchai Looareesuwan[1], Tran Tinh Hien[8], Jeremy Farrar[9], François Nosten[1,2,10], Nicholas PJ Day[1,2], Nicholas J White[1,2*]**

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**TO** determine the optimum duration of follow-up for the assessment of drug efficacy against *Plasmodium falciparum* malaria, 96 trial arms from randomized controlled trials (RCTs) with follow-up of 28 days or longer that were conducted between 1990 and 2003 were analyzed. These trials enrolled 13,772 patients, and participating patients comprised 23% of all patients enrolled in RCTs over the past 40 years; 61 (64%) trial arms were conducted in areas where the rate of malaria transmission was low, and 58 (50%) trial arms were supported by parasite genotyping to distinguish true recrudescences from reinfections. The median overall failure rate reported was 10% (range, 0 to 47%). The widely used day 14 assessment had a sensitivity of between 0 and 37% in identifying treatment failures and had no predictive value. Assessment at day 28 had a sensitivity of 66% overall (28 to 100% in individual trials) but could be used to predict the true failure rate if either parasite genotyping was performed ($r2 = 0.94$) or if the entomological inoculation rate was known. In the assessment of drug efficacy against falciparum malaria, 28 days should be the minimum period of follow-up.

Wellcome Trust-Mahidol University-Oxford Tropical Medicine Research Programme funded by the Wellcome Trust of Great Britain.
**Published in:** *Antimicrobial Agents and Chemotherapy* 2004;48:4271-80.

# THE DEFORMABILITY OF RED BLOOD CELLS PARASITIZED BY *PLASMODIUM FALCIPARUM* AND *P. VIVAX*

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**RED** blood cells (RBCs) must deform considerably during their multiple passages through the microvasculature and the sinusoids of the spleen. RBCs infected with *Plasmodium falciparum* (Pf-IRBCs) become increasingly rigid as they mature but avoid splenic clearance by sequestering in venules and capillaries. In contrast, RBCs infected with *P. vivax* (Pv-IRBCs) do not sequester. We compared the effects of *P. vivax* and *P. falciparum* infection on RBC deformability in a laminar shear flow system. Pf-IRBCs became more rigid as the parasite matured, but equivalent maturation of Pv-IRBCs resulted in a doubling of flexibility. Coincidentally, the IRBC surface area increased from 56.7 ± 1.3 m2 to 74.7 ± 0.6 m2 to 90.9 ± 1.1 m2 in ring-, trophozoite-, and schizont-stage Pv-IRBCs, respectively, whereas Pf-IRBCs did not increase in size. *P. vivax* increases the deformability of IRBCs and thereby avoids splenic entrapment.

Wellcome Trust-Mahidol University-Oxford Tropical Medicine Research Programme funded by the Wellcome Trust of Great Britain.
**Published in:** *The Journal of Infectious Diseases* 2004;189:190-4.

# AN OPEN, RANDOMISED, CONTROLLED TRIAL OF PENICILLIN, DOXYCYCLINE, AND CEFOTAXIME FOR PATIENTS WITH SEVERE LEPTOSPIROSIS

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**BACKGROUND.** Leptospirosis is an important cause of fever in the rural tropics. Since 1996, there has been a marked increase in the incidence of leptospirosis in northeastern Thailand. Although leptospirosis generally is susceptible to antibiotics, there is no consensus regarding the optimal Treatment for severe leptospirosis.

*Methods.* An open-label, randomized comparison of parental cefotaxime, penicillin G sodium (hereafter known as "penicillin G"), and doxycycline for the treatment of suspected severe leptospirosis was conducted. The study involved 540 patients admitted to 4 hospitals in northeastern, Thailand.

*Results.* A total of 264 patients (48.9%) had leptospirosis confirmed by serologic testing or culture. The overall mortality rate was 5%. There were no significant differences between the antibiotics with regard to associated mortality, defervescence, or time to resolution of abnormal findings of laboratory tests either among all study participants or among the subgroup of patients with confirmed leptospirosis. A total of 132 patients had rickettsial infection diagnosed, and, for these patients, treatment with doxycycline was superior to treatment with penicillin G.

*Conclusions.* Doxycycline or cefotaxime is a satisfactory alternative to penicillin G for the treatment of severe leptospirosis.

Wellcome Trust-Mahidol University-Oxford Tropical Medicine Research Programme funded by the Wellcome Trust of Great Britain.
**Published in:** *Clinical Infectious Diseases* 2004;39:1417-24.

# EVALUATION OF IMMUNOGLOBULIN M (IgM) AND IGG RAPID CASSETTE TEST KITS FOR DIAGNOSIS OF MELIOIDOSIS IN AN AREA OF ENDEMICITY

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**AN** enzyme-linked immunosorbent assay-based rapid cassette immunoglobulin G (IgG) and IgM immunochromogenic test kit was compared to the indirect hemagglutination test (IHA) for the diagnosis of acute melioidosis in northeastern Thailand. Admission sera from 70 culture-confirmed septicemic melioidosis patients and 30 patients with localized infections were tested. As a control group, 80 patients with other acute febrile illnesses (other bacterial infections, leptospirosis, or scrub typhus) and 119 healthy individuals were tested. The diagnostic sensitivity of the IgG and IgM tests and the IHA test were 79, 67, and 72%, respectively, with corresponding specificities of 90, 80, and 68%. This kit represents an improvement over IHA for the diagnosis of melioidosis an area of endemicity although, as with other serological tests, it has reduced diagnostic utility in a population with high background seropositivity.

Wellcome Trust-Mahidol University-Oxford Tropical Medicine Research Programme funded by the Wellcome Trust of Great Britain.
**Published in:** *Journal of Clinical Microbiology* 2004;42:3435-7.

# ANTIMALARIAL DRUG RESISTANCE, ARTEMISININ-BASED COMBINATION THERAPY, AND THE CONTRIBUTION OF MODELING TO ELUCIDATING POLICY CHOICES

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**INCREASING** resistance of *Plasmodium falciparum* malaria to antimalarial drugs is posing a major threat to the global effort to çRoll Back Malariaé. Chloroquine and sulfadoxine-pyrimethamine (SP) are being rendered increasingly ineffective, resulting in increasing morbidity, mortality, and economic and social costs. One strategy advocated for delaying the development of resistance to the remaining armory of effective drugs is the wide-scale deployment of artemisinin-based combination therapy. However, the cost of these combinations are higher than most of the currently used monotherapies and alternative non-artemisinin-based combinations. In addition, uncertainty about the actual impact in real-life settings has made them a controversial choice for first-line treatment. The difficulties in measuring the burden of drug resistance and predicting the impact of strategies aimed at its reduction are outlined, and a mathematical model is introduced that is being designed to address these issues and to clarify policy options.

Wellcome Trust-Mahidol University-Oxford Tropical Medicine Research Programme funded by the Wellcome Trust of Great Britain.
**Published in**: *The American Journal of Tropical Medicine and Hygiene* 2004; 71 supplement 2: 179-86.

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