

Dynamic changes of malaria epidemiology in Southeast Asia and South Pacific area and researches for next steps of control

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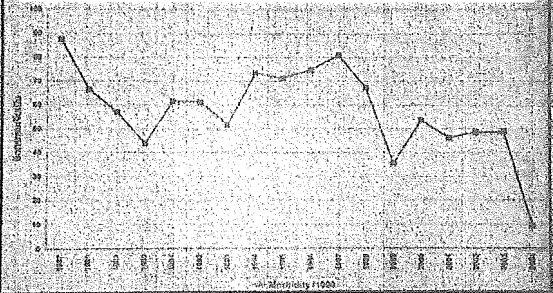
Project title: Construction of net work on epidemiology and control of malaria in Asia and South Pacific area

Introduction: Because of the recent progress of malaria control, mortality and morbidity due to *Plasmodium* infection have dramatically decreased in Asia and South Pacific area. This change in epidemiology has resulted in inadequacy of the indicators and systems that had been used for many years. Drug resistant malaria still poses a significant public health threat to the world. The design and incorporation of chemotherapeutic intervention may be essential for the next step of malaria control. In order to promote communication and exchange of the information of malaria, network of institutes among Asian countries and South Pacific areas should be constructed and strengthened.

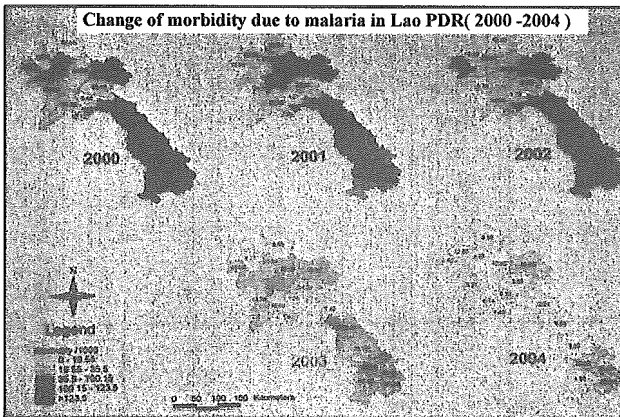
Dynamic changes in epidemiology of malaria in Southeast Asia

Because of the success of big malaria control program such as Mekong malaria control, morbidity and mortality due to *Plasmodium* infection have dramatically improved in Southeast Asia. Before the beginning of Mekong malaria control program, successful cases of malaria control had been reported in Vietnam and Thailand. Decrease of morbidity and mortality has been recently reported in Cambodia, Lao PDR and Myanmar.

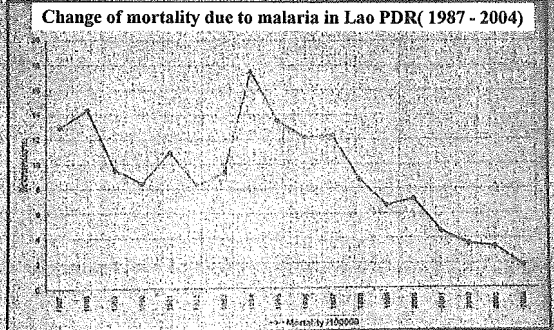
Change of morbidity due to malaria in Lao PDR (1987-2004)



Change of morbidity due to malaria in Lao PDR (2000-2004)



Change of mortality due to malaria in Lao PDR (1987-2004)

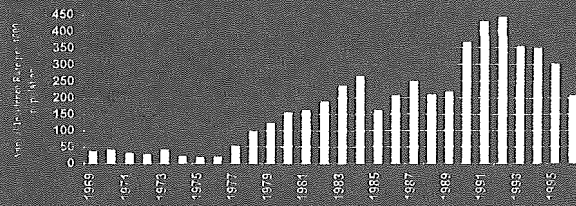


Dynamic changes in epidemiology of malaria in South Pacific islands

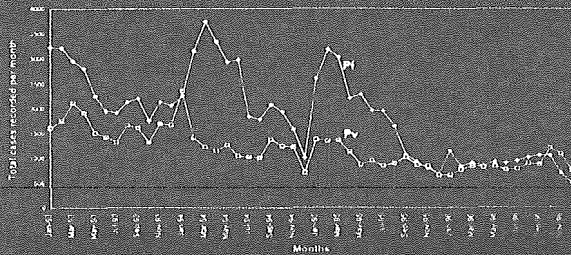
Some south pacific countries such as Papua New Guinea and Solomon Islands have been known as heavy endemic areas of malaria. But symptoms of *P. falciparum* infection are moderate in this area, and this situation has been reported as Pacific enigma (Holo- or hyper endemic area but low mortality and low morbidity, Maitland K. et al., 1997, 1998. Sanual A. et al., 1998).

Because of intensive malaria control program in the 1990s, annual incidence of malaria has decreased in Solomon Islands. Prior to distribution of insecticide treated bed net in 1994 and 1995, chemotherapeutic intervention has used since 1996.

Change of annual incidence rate of malaria in the Solomon Islands (1969 – 1996)

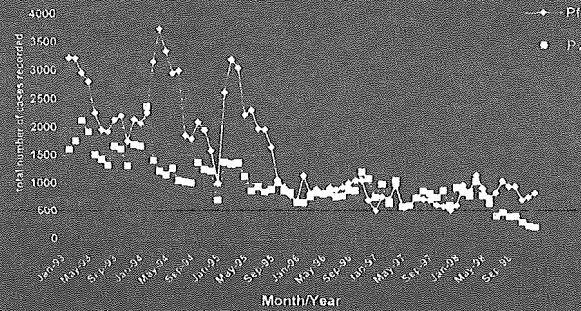


Change of malaria cases in Honiara, the Solomon Islands



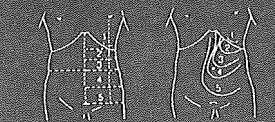
Selective mass treatment with chloroquine was introduced in the beginning of rainy season (January and February) of 1996. The number was detected by passive case detection (PCD).

Change of Malaria parasite trends in Honiara, the Solomon Islands



Selective mass treatment with chloroquine and primaquine was introduced in the beginning of rainy season of 1998. The number was detected by PCD.

Hackett's Spleen Rate: a indicator to detect endemicity of malaria

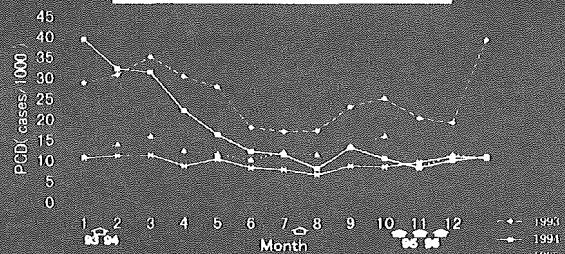


Classification of spleen size according to Hackett. A. Topographical reference lines for the five classes of enlarged spleen. B. Projection on the surface of the abdomen of the five classes of enlarged spleen.

The endemicity of malaria can be classified on the following basis:

1. Hypoendemic malaria with spleen rate of 0-10%.
2. Mesoendemic malaria with spleen rate of 11-50%.
3. Hyperendemic malaria with spleen rate consistently over 50%. The spleen rate in adults is also high.
4. Holoendemic malaria with spleen rate constantly over 75%. The spleen rate in adults is low; it is in this type of endemicity that the strongest adult tolerance is found.

Seasonal change of malaria in a rural village in the Solomon Islands



Selective mass treatment with Chloroquine was conducted in Jan. - Feb. 1993 & 1994, or Nov. - Dec. 1995 & 1996. The number was detect by PCD.

Progress of malaria control program and changes of indicators to detect the endemicity in a rural village of Solomon Islands

	Aug. 93	Jan. 94	Jan. 95	Jan. 96	Dec. 96	Jan. 98
Parasite rate						
2 - 9	70.6	71.8	62.3	44.3	42.3	32.3
2 - 14	64.3	65.8	57.7	41.3	36.8	28.9
Accuracy of clinical diagnosis						
Sensitivity	36.7	32.5	18.9	15.4	11.1	10.2
Specificity	59.1	73.0	83.5	90.0	93.3	94.2
Spleen rate						
Hackett	76.1	23.6	19.0	12.0	10.3	9.7
Detection by US	77.5	64.2	52.3	40.5	34.2	25.5

%

Malaria control program and its success in the Solomon islands.

- The first step (1994, 1995) Use of insecticide treated bed net
Effect Decrease of symptomatic malaria patients
No change of seasonal trends in the number of malaria patients
- The second step (1996-1998) Use of insecticide treated bed net +
Selective mass treatment in the beginning of rainy season
Effect Decrease of symptomatic malaria patients
No dynamic decrease of parasite rates
No seasonal trends in the number of malaria patients

Because of ethnic tension, they had no national control program of malaria since 1999 to 2002. They have recently had no big re-emerging of *P. falciparum* infection.

Chemotherapeutic control program and dynamic change in malaria epidemiology

- After the introduction of selective mass treatment with Chloroquine, the number of *P. falciparum* infection has dramatically decreased. But the number of *P. vivax* infection has not decreased.
- After the intensive chemotherapeutic intervention with Chloroquine, parasite rate has not decreased dramatically. Passive case detection(PCD) by reportin from clinics and hospitals was not enough to detect the endemicity of malaria.
- And some indicators such as Hackett' s spleen rates and febrile or shivering episodes among village people have become insufficient to detect the endemicity of malaria.
- After the introduction of selective mass treatment with chloroquine and Primaquine, the number of *P. vivax* infections has decreased.

Change in the trends of imported cases of malaria in Japan (1984 - 1998)

year	Pf				Pv				Po total country	Pm total country
	Africa	Southeast Asia	South Asia	South America	Africa	Southeast Asia	South Asia	South America		
1984	6	0	0	0	2	0	6	0		
1985	3	2	1	0	1	2	2	0		
1986	4	2	0	0	1	5	5	0	2	2
1987	2	2	1	0	2	0	3	0		
1988	8	1	1	0	1	3	3	0		
1989	6	3	0	0	1	2	3	0		
1990	3	1	1	0	3	4	6	2		
1991	6	4	0	1	0	6	3	0		
1992	3	1	1	0	0	0	6	0		
1993	7	0	1	0	1	6	1	0		
1994	8	2	3	0	2	1	3	1		
1995	6	1	0	0	0	1	1	0		
1996	8	2	0	0	1	1	3	1		
1997	16	1	1	0	5	6	5	3		
1998	23	4	0	0	3	3	3	0		
total	106	31	10	1	23	39	82	7	2	2

The patients with >0.1% parasitemia are listed.

Imported cases of *P. falciparum* infection from Southeast Asian and South Pacific countries.

Pf	Myanmar	Lao	Thailand	Philippines	Indonesia	PNG	Africa
1984							5
1985				2			3
1986					1		4
1987						1	2
1988							8
1989			1		2		5
1990				1			3
1991			2	1	1		6
1992				1			3
1993							7
1994		1			1		8
1995					1	1	6
1996				1		2	8
1997	1						15
1998		3	1		1	3	23
Total	1	4	4	7	7	11	106

The patients with >0.1% parasitemia are listed.

Imported cases of *P. vivax* infection from Southeast Asian and South Pacific countries

	Myanmar	Laos	Thailand	Singapore	China	Taiwan	Philippines	Indonesia	PNG	Africa
1984			1							2
1985								1		1
1986			2		1	1(?)	1		2	1
1987										2
1988			1		1		1			1
1989								1	1	1
1990								2	2	3
1991	4		1							
1992										
1993			1					1	3	1
1994				1(?)						2
1995									1	
1996		1	1							1
1997	1		1	1(?)				4	1	5
1998								2	1	3
Total	6	1	8	2(?)	2	1(?)	3	11	11	23

The patients with >0.1% parasitemia are listed.

The trend in imported cases of *P. vivax* infection from South Asian countries

	India	Sri Lanka	Nepal	Pakistan
1984	3(gh)	1(h)	2(h)	1
1985	1			1
1986	3(j)		1(j)	2
1987	1	1		1
1988	3			
1989	2			1
1990	4	1	1	
1991	2			1
1992	4(k)	1	1(k)	
1993	1			
1994	3	1(l)		
1995	1			
1996	3			
1997	5			
1998	3			
total	39	5	5	7

The case with >0.1% parasitemia was listed

Change in the trends of imported cases of malaria in Japan

- The number of imported cases of *P. falciparum* from Africa has recently shown rapid increase. Most of the imported cases of *P. falciparum* infection are from Africa.
- In spite of rapid increase of the number of people going South Asian countries, the number of imported cases of malaria from this area has not increased.
- We have had some imported cases of *P. vivax* infection from South Asian countries, especially from India.

Useful information for network system on malaria and next step of control

- Dynamic change of epidemiology
 - Seasonal or local trends of malaria infection
 - Change of morbidity
 - The shift from symptomatic severe cases to asymptomatic moderate cases.
 - The shift from *P. falciparum* infection to *P. vivax* infection
 - Molecular basis for difference of morbidity and drug resistance
 - Necessity of new indicators and investigation on molecular and pathological basis of new investigators
- PCD and some present indicators are not enough to detect dynamic change of epidemiology. Further investigation are necessary on new indicators to detect the endemicity of malaria and good combination of PCD and ACD. Adequate monitoring system is expected for low malaria endemicity.

Useful information for network system on malaria and next step of control

- The role of chemotherapeutic intervention
 - Targeting population, Best season, Duration, Frequency, Choice of anti-malarial agents
- Standardization of system for treatment
 - Detection of drug resistance
 - Detection of G6PD deficiency
- Mathematical modeling
 - Good control plan from the socioeconomic aspects
 - Prevention of re-emerging

We express sincere thanks for the colleagues in Lao PDR and the Solomon Islands, participants of this meeting and financial support.

Thank you again

Mathematical model of Malaria transmission and control

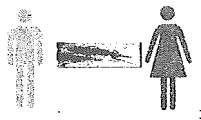
Re-emerging of vivax in Korea

Kazutoshi Fujita, Hirofumi Ishikawa
 Graduate School of Environmental science,
 Okayama Univ.
 Jan 31-Feb 1, 2006, at NIID

Mathematical model of *P. vivax*

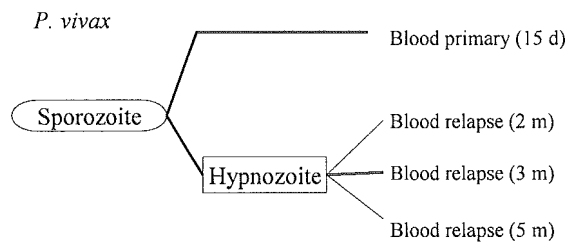
Plasmodium vivax Malaria

- Transmission Process
 - Indirect Transmission
 - Influenced by Mosquito Density & Seasons
- Relapse
 - Hypnozoites



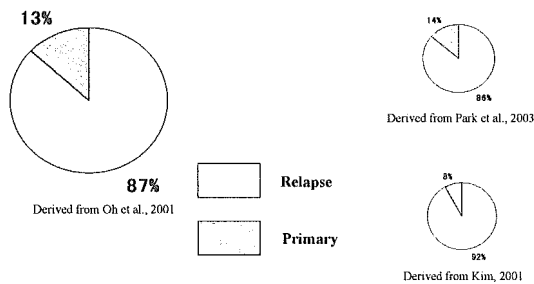
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Exoerythrocytic development



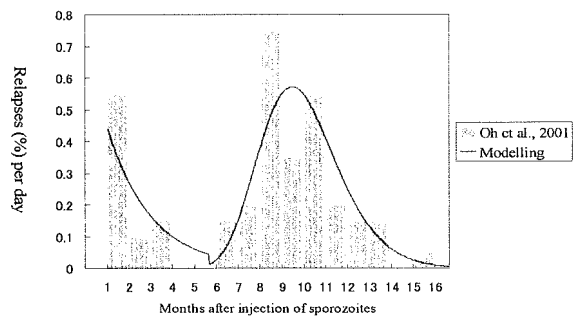
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Ratio of Primary infection to Relapse

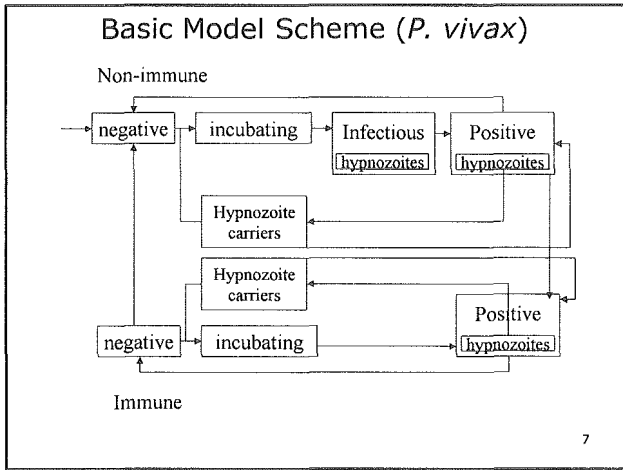


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The distribution of the latent period of relapses in South Korea

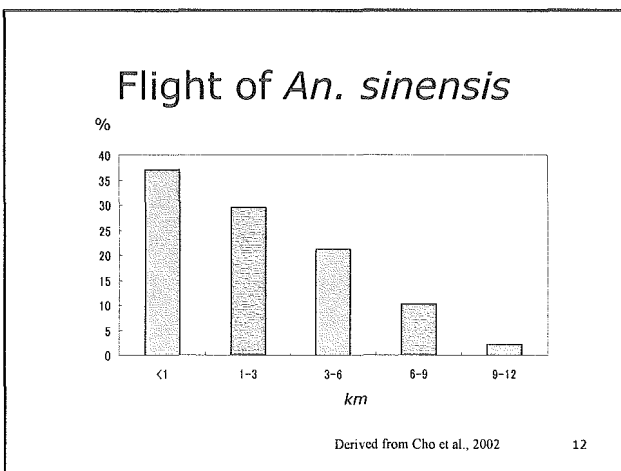
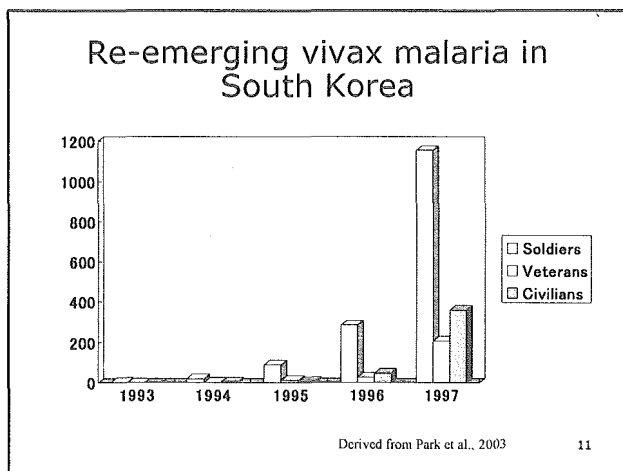
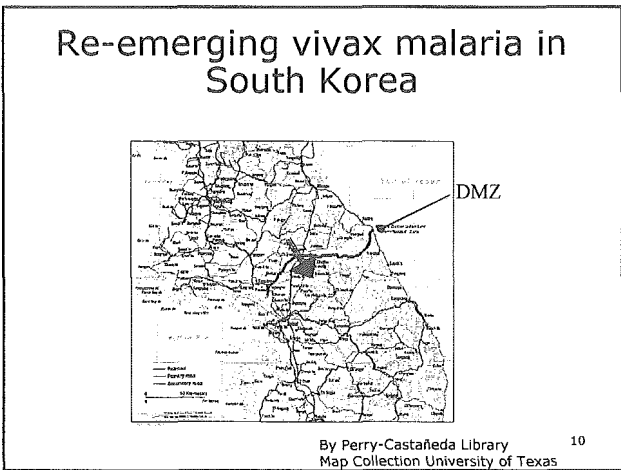
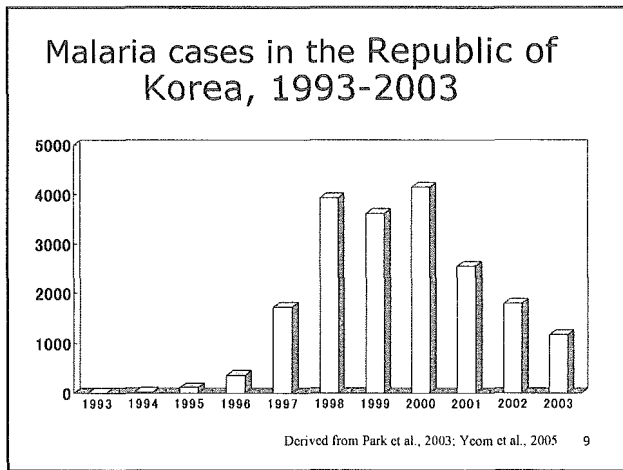


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Re-emerging *Plasmodium vivax* malaria in Demilitarized Zone, Korea

Presumption

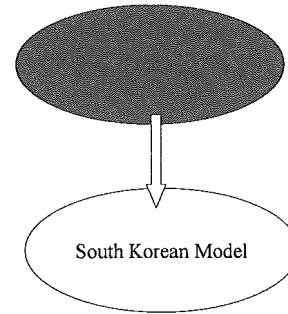


Korean Model

Construction of North Korean Model & South Korean Model

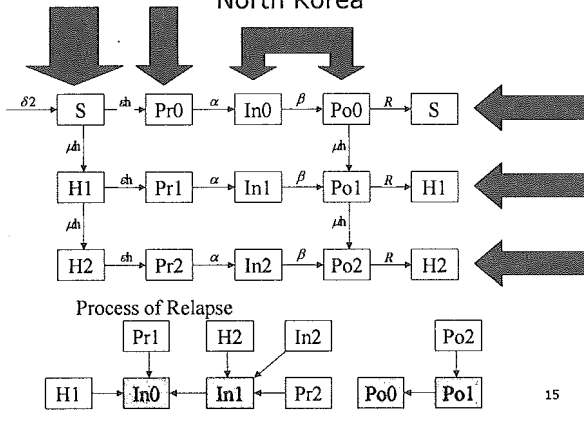
N. K. Model operates on S. K. Model one-sidedly

Malaria Models for DMZ



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Scheme of malaria model for North Korea



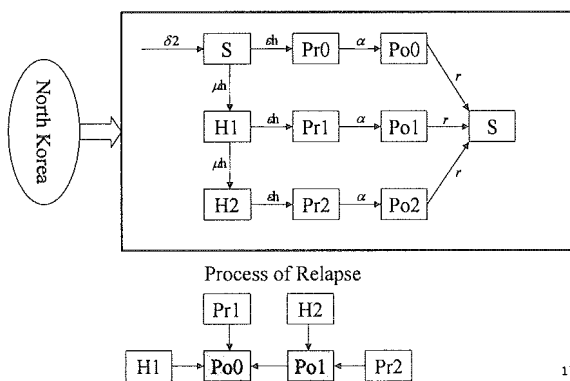
15

Features of South Korean model

- State of medical treatment for malaria in South Korea
 - All patients are dosed with chloroquine and treated radical cure, then they are cured and have no hypnozoites.
- Influence of the prevalence in North Korea
 - The influence depends on the distance from DMZ to the target region.

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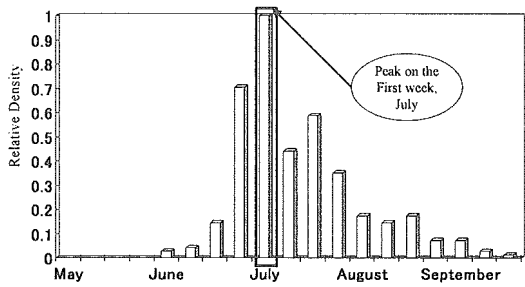
Scheme of malaria model for South Korea



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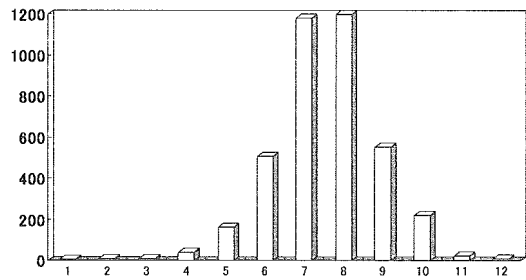
Seasonal variation in malaria incidence

Seasonal variation in the density of *An. sinensis*



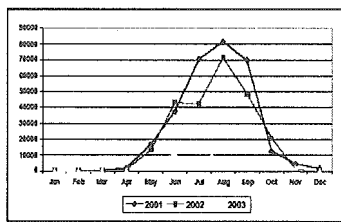
Derived from Lee et al., 2002 19

Number of reported cases of malaria in South Korea, by month, in 1998



Derived from NIH Korea, 2003 20

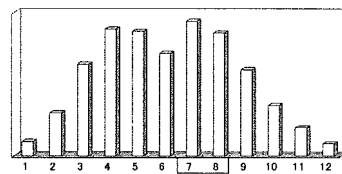
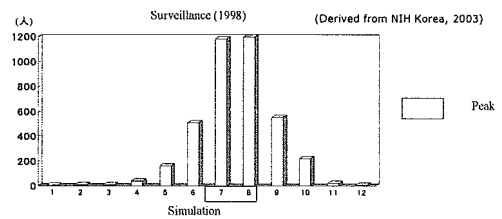
Number of reported cases of malaria in DPR Korea, by month, in 2001-2003



Derived from Vason Pinyowiwat
Medical Officer, CDS/CSR WR Office, DPR Korea

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Variation of Incidences by month

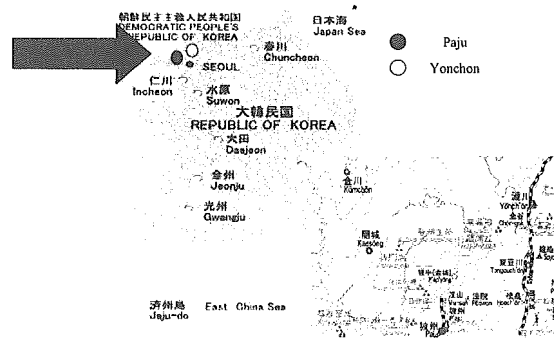


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Simulation

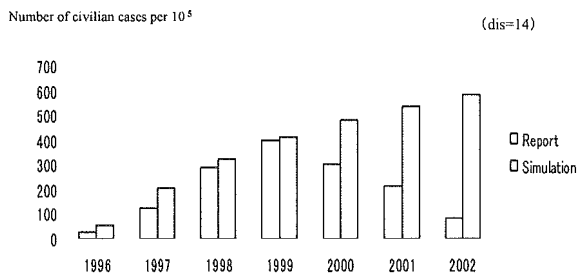
Yonchon, Paju
near DMZ in South Korea

Study Areas



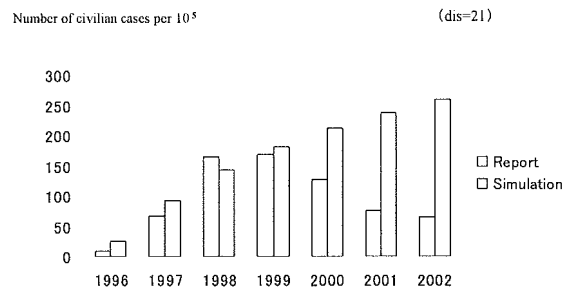
24

Yonchon in South Korea



Derived from CDMR 2003; Moon 2001; Lee 1998; Park 2003 25

Paju in South Korea



Derived from CDMR 2003; Moon 2001; Lee 1998; Park 2003 26

Reduction Factors of malaria cases

Reduction factor ①

- Shortening the Diagnosis period

Year	1995	1997	1999	2000
Diagnosis period (days)	23.6	13.6	11	5

Derived from Lee et al., 1998; Lee et al., 2001

28

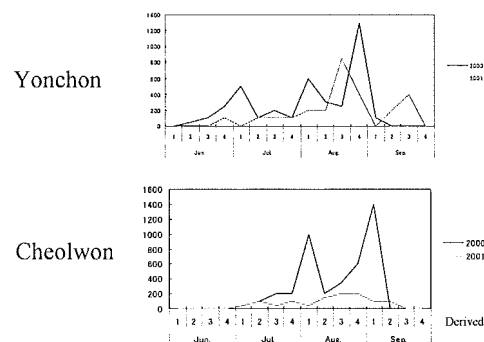
Reduction factor ②

- Reduction of mosquito density in 2001

➤ The persistence of dry weather caused a drastic retrenchment of mosquito density in 2001 in Korea

29

Reduction of mosquito density



Derived from Yoon et al., 2005

30

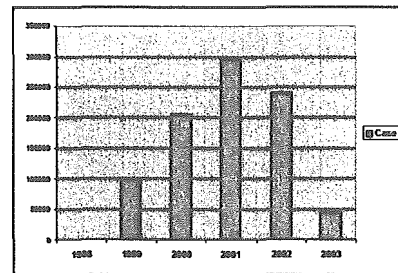
Reduction factor ③

- Reduction in prevalence of malaria in DPR Korea
 - National malaria control activities started in DPR Korea in 1999 based on Roll Back Malaria Program (WHO).
 - R Korea gave assistance \$500,000 in 2000.

Derived from Chol et al., 2005

31

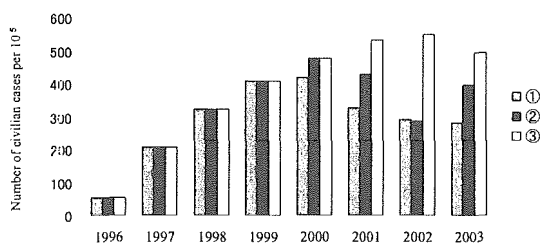
Number of reported cases of Malaria in DPR Korea, by year, 1998-2003



Derived from Vason Pinyowiat
Medical Officer, CDS/CSR WR Office, DPR Korea

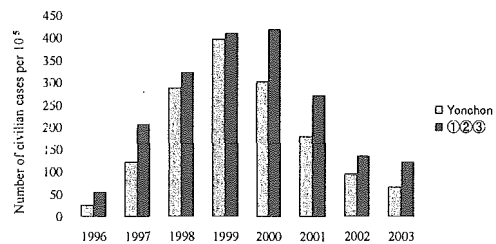
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Comparison among reduction factors



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Simulation under 3 reduction factors



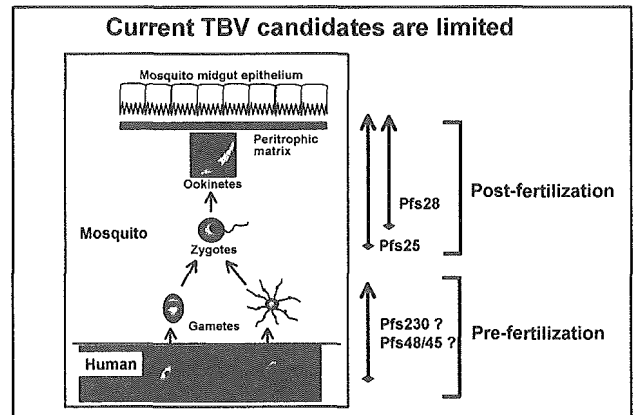
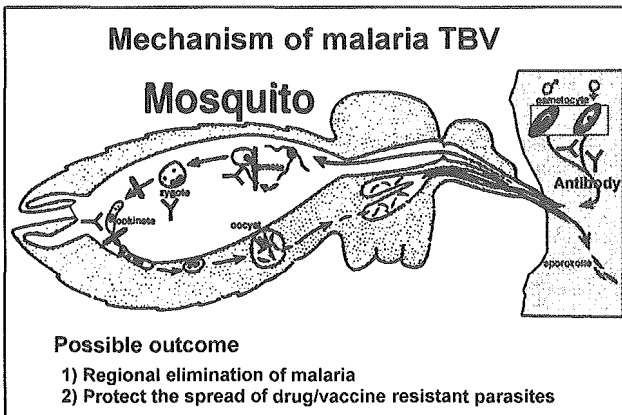
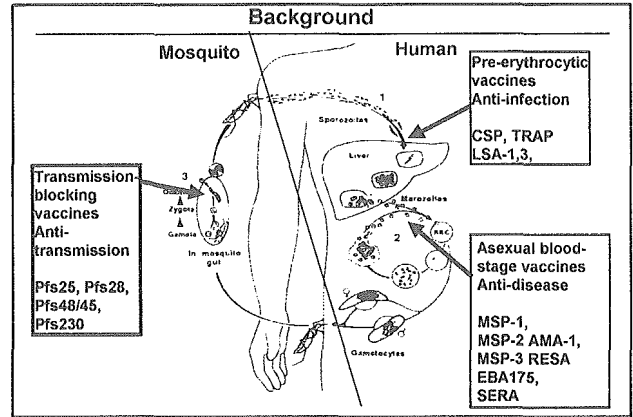
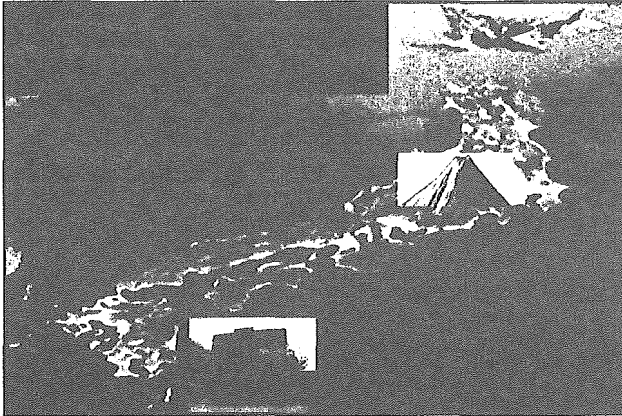
Derived from CDMR 2003; Moon 2001; Lee 1998; Park 2003

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Conclusion

- Construction of mathematical models for transmission of vivax malaria near DMZ regions
- Simulating the process of re-emerging malaria in several regions (Paju, Yonchon)
- Estimating the control factors on the prevalence of malaria

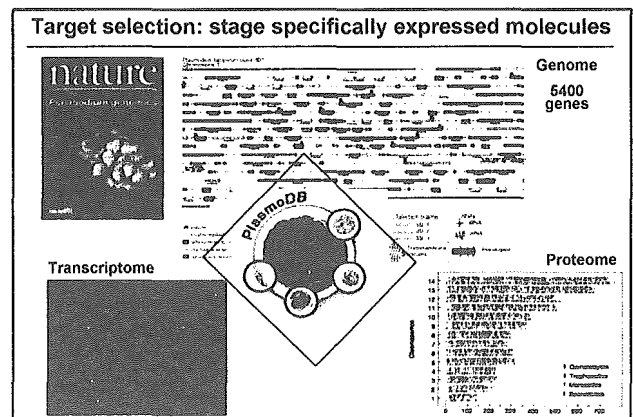
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Aim

Novel antigen discovery for Transmission-blocking vaccines:

Post-genome approach

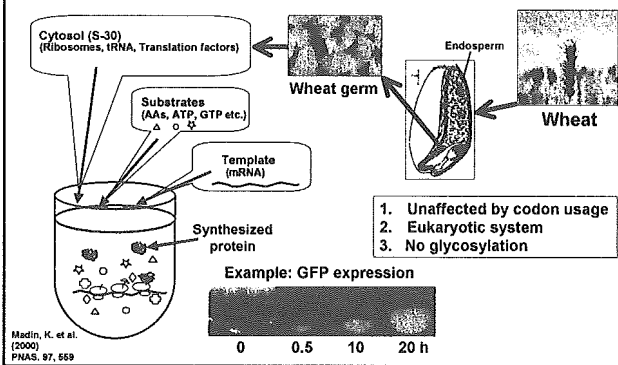


Methods

- How to do?
 - Recombinant protein expression
- Requirement for the protein expression method
 - Not affected by codon usage
 - Proper folding is necessary
 - No glycosylation
- Traditional methods are contradictory
 - *E. coli*, Yeast, Insect cell, virus, etc.
- Selection of protein expression system
 - **TRY NEW METHOD!**
 - *Wheat germ cell-free system*

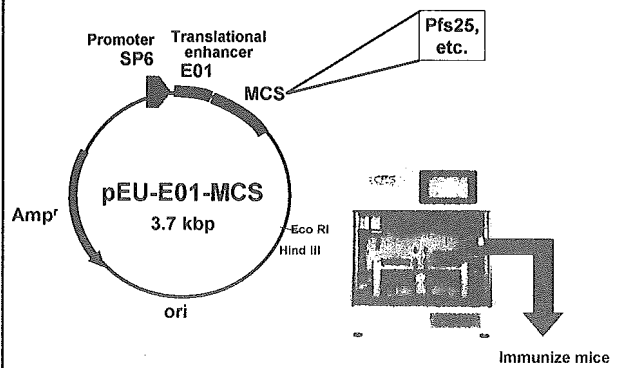
- What is wheat germ cell-free expression system?
- Proof-of-principle : Pfs25 expression
- Genome wide expression of falciparum proteins
- Screening strategy of novel TBV candidates

Wheat Germ Cell-free Protein Expression System

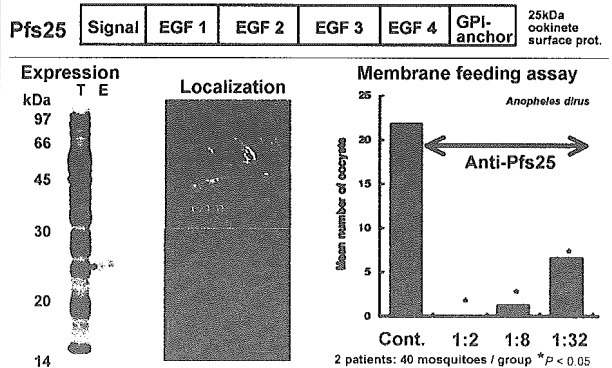


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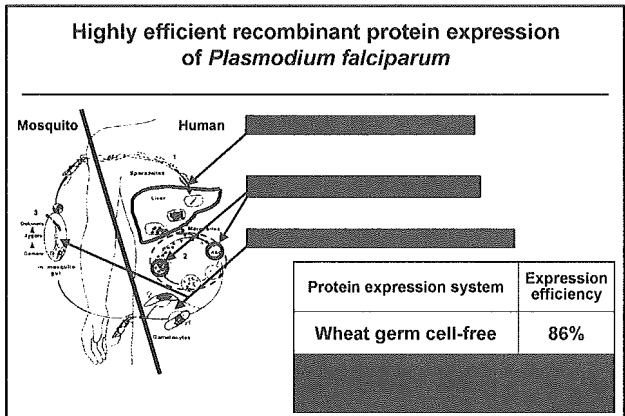
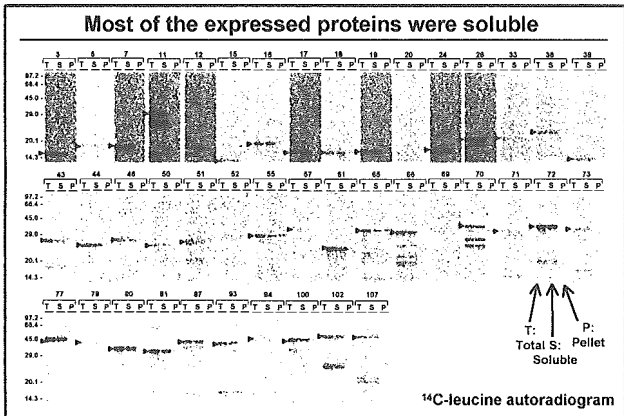
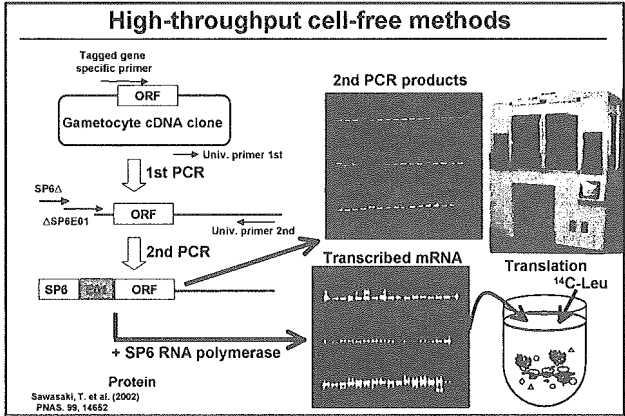
Large scale wheat germ cell-free expression



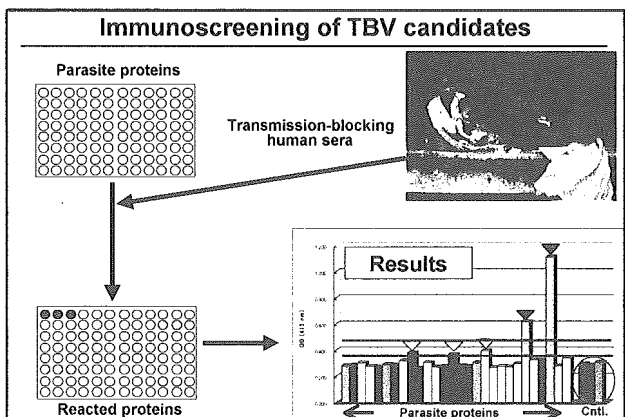
Anti-Pfs25 sera completely block transmission of *P. falciparum*



- What is wheat germ cell-free expression system?
- Proof-of-principle : Pfs25 expression
- Genome wide expression of falciparum proteins
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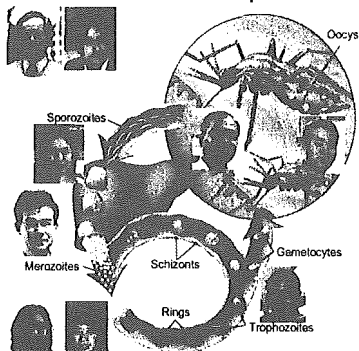


Summary and Perspectives

1. Wheat germ cell-free system is an efficient tool for the genome-wide recombinant protein expression of falciparum molecules.
2. High-throughput screening of novel malaria transmission-blocking vaccine candidates is feasible.
3. This high-throughput method is also applicable to novel antigen discovery from all the stages.

Acknowledgments

CSTRC Malaria Group



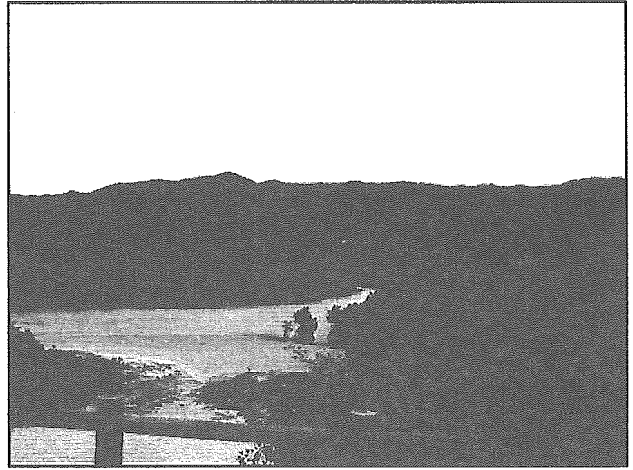
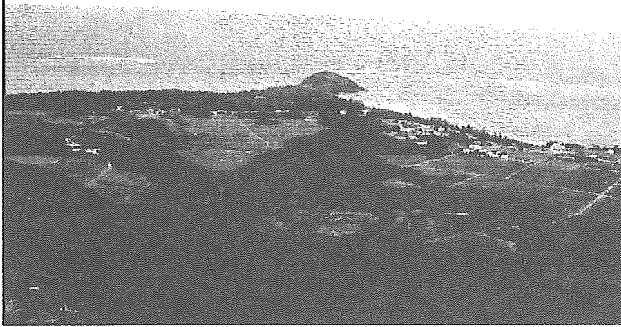
MVDB, NIAID, NIH
Sanjay Singh, David Keister,
Carole Long, Allan Saul

AFRIMS, Thailand
Jetsumon Sattabongkot

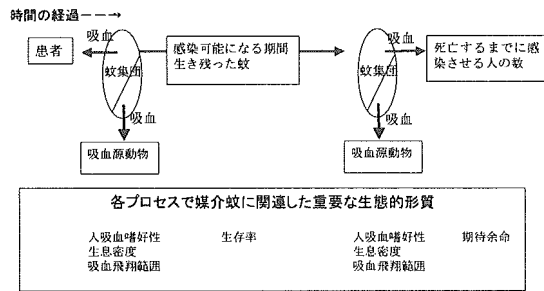
Facul. Sci. Mahidol Univ., Thailand
Rachanee Udomsangpetch

Financial support
Ministry of Health, Labour and
Welfare, Japan

我が国におけるマラリア媒介蚊の生息状況



2次患者が発生するプロセス



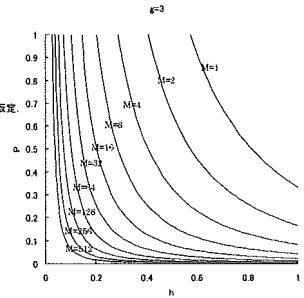
媒介蚊の生態的形質の相互関係に関する理論的推測

蚊の生息密度, M
 人嗜好性, h
 感染可能になるまで生き残る割合, P
 感染可能にするまでに行う吸血の回数, g
 情報のために、患者から吸血した蚊は必ず感染すると仮定。

1人の患者によって感染した蚊が死亡するまでに行う人への吸血回数(=2次患者の発症数) $= M \cdot h^2 \cdot P \cdot g$

マラリアが流行するためには、1人の患者から1人以上の2次患者が発生することが条件。

$$M \cdot h^2 \cdot P \cdot g > 1$$

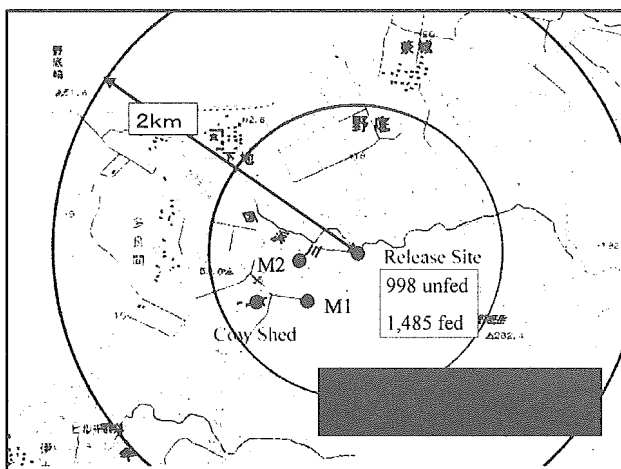
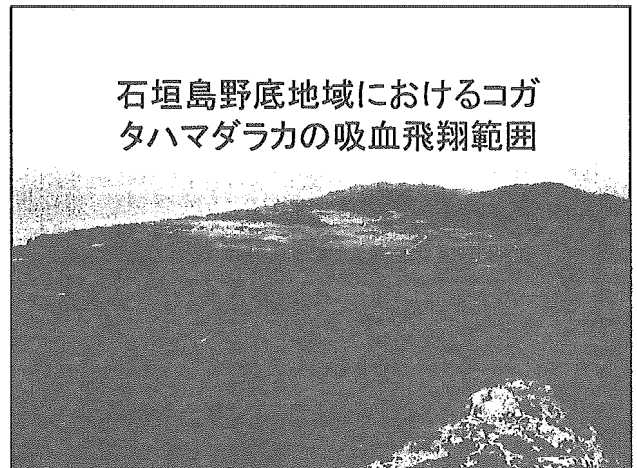
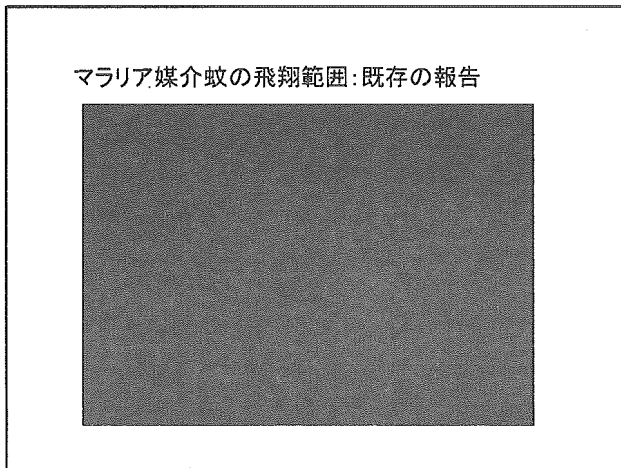
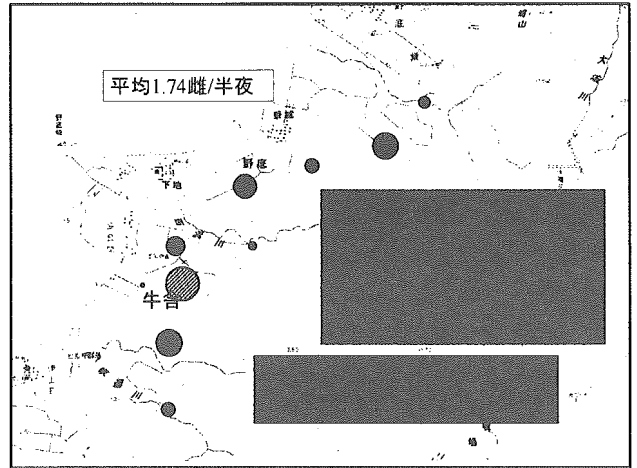
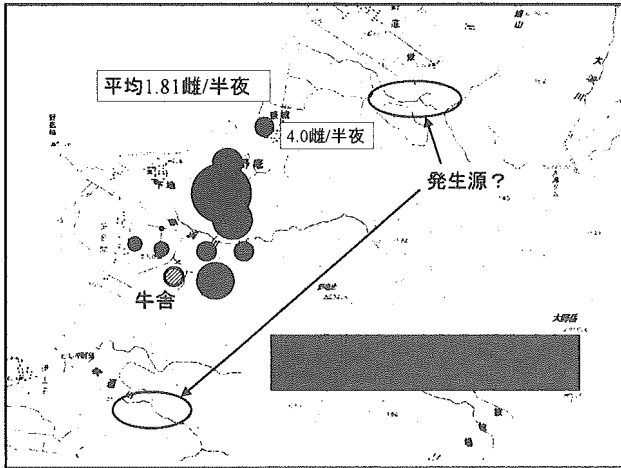


人嗜好性やマラリア原虫媒介能を考慮すると、我国産12種のハマダラカでその分布や生息密度を問題とすべき種類は5種類である。

コガタハマダラカ	<i>Anopheles (Cel.) minimus</i>	琉球列島 (宮古, 八重山群島)
オオハマハマダラカ	<i>An. (Ano.) soperoi</i>	琉球列島 (沖縄, 八重山群島)
シナハマダラカ	<i>An. (Ano.) sinensis</i>	北海道, 本州, 四国, 九州, 対馬, 屋久島, 琉球列島, 大東諸島,
オオツルハマダラカ	<i>An. (Ano.) lesteri</i>	北海道, 本州, 九州, 琉球列島 (奄美, 沖縄, 八重山群島)
チョウセンハマダラカ	<i>An. (Ano.) coreicus</i>	北海道, 本州, 四国, 九州

琉球列島のハマダラカ



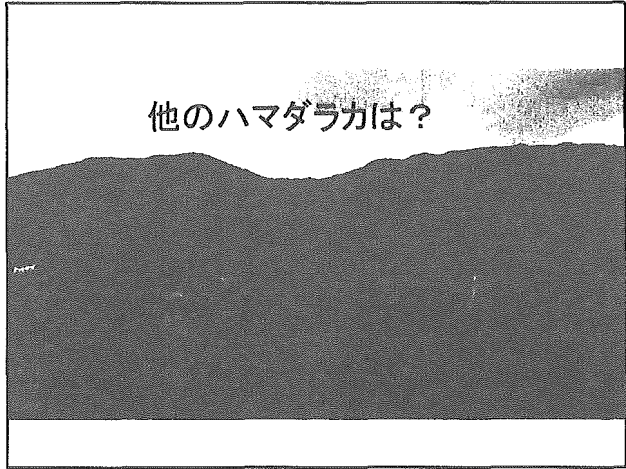
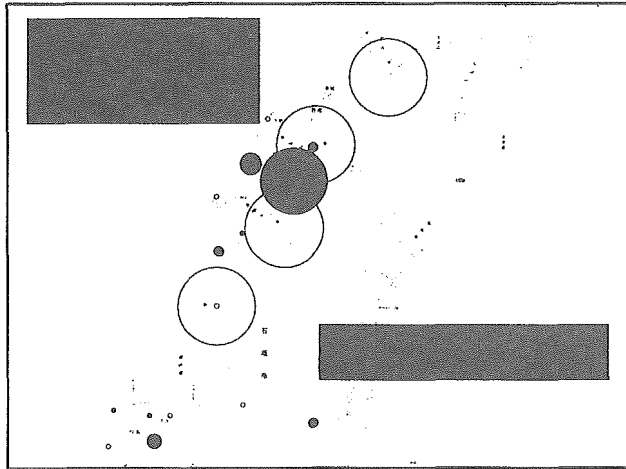
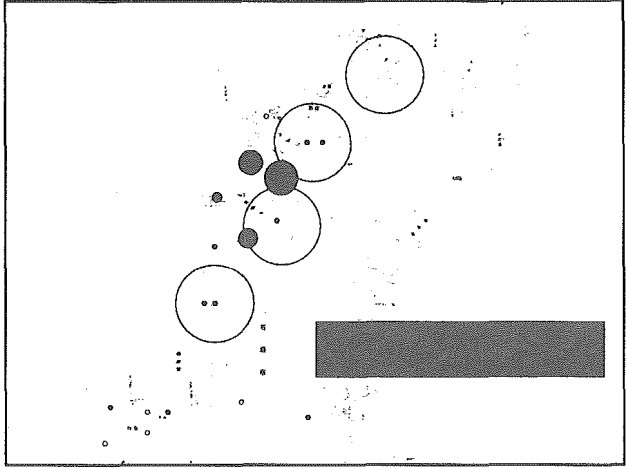
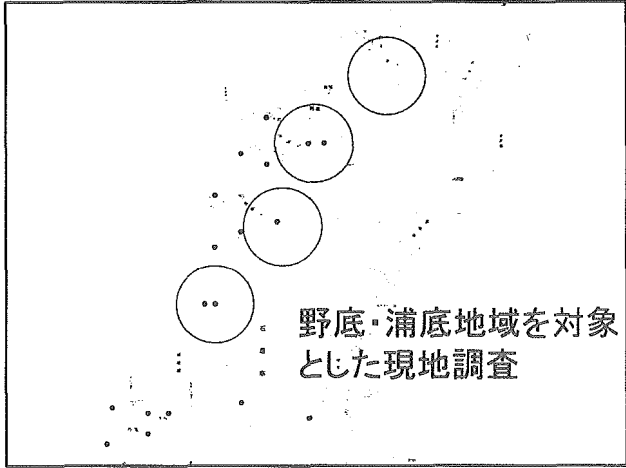
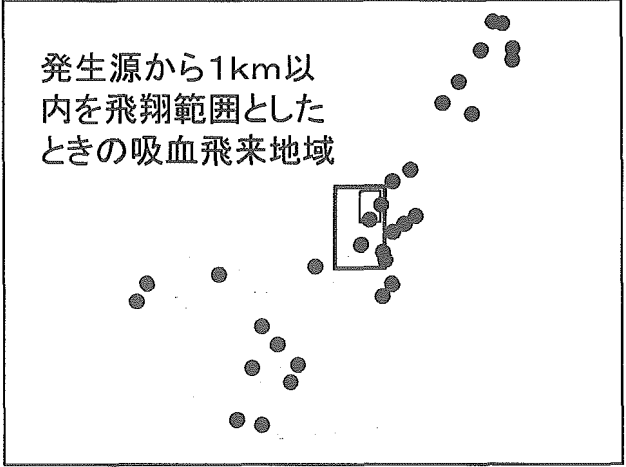
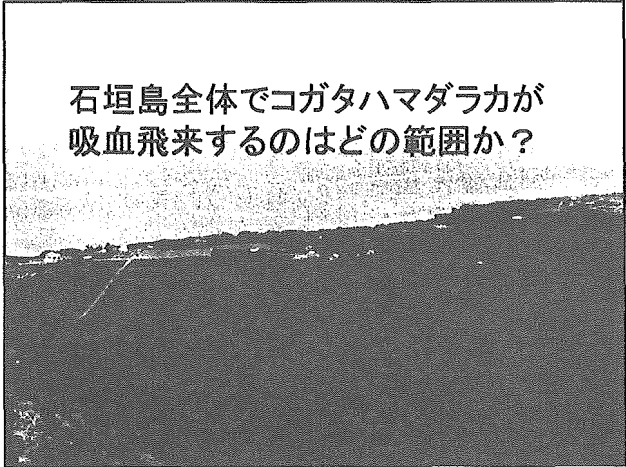


September 1999 TSUDA ET AL.: MARK-RELEASE-RECAPTURE OF *An. minimus* IN JAPAN 603

Table 1. Number of marked and unmarked *An. minimus* collected at 4 sites in March 1993 on Itoya Island, Japan

Cohort	Collection site	Collection method*	Days after release					Total
			0	1	2	3	4	
Fed	Release	Human bait	4	10	2	1	0	17
	Middle 1	Human bait	0	6	0	4	1	11
	Middle 2	Human bait	1	1	0	0	1	3
	Cowshed	Human bait	0	2	0	0	0	2
		Sweeping	0	0	0	2	0	2
		Light trap	0	5	0	0	0	5
	Total		5	26	2	7	2	42
Unfed	Release	Human bait	6	0	1	0	0	7
	Middle 1	Human bait	0	1	0	0	1	2
	Middle 2	Human bait	0	0	0	0	1	1
	Cowshed	Human bait	0	0	0	0	0	0
		Sweeping	0	1	0	0	0	1
		Light trap	0	2	0	0	0	2
	Total		6	4	1	0	2	13
Unmarked	Release	Human bait	1	0	0	0	1	2
	Middle 1	Human bait	0	1	2	7	2	12
	Middle 2	Human bait	0	0	0	0	0	0
	Cowshed	Human bait	0	0	0	0	0	0
		Sweeping	1	2	0	2	1	6
		Light trap	0	0	0	0	0	0
	Total		2	3	2	9	4	20

* Sweeping and light trap collections were conducted only at the cowshed.



1998-2005年

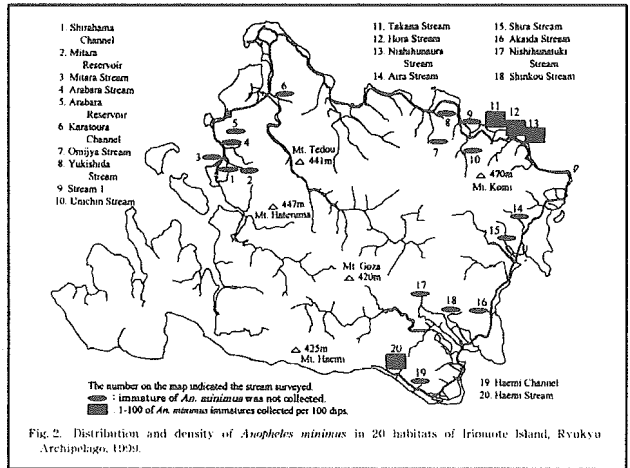
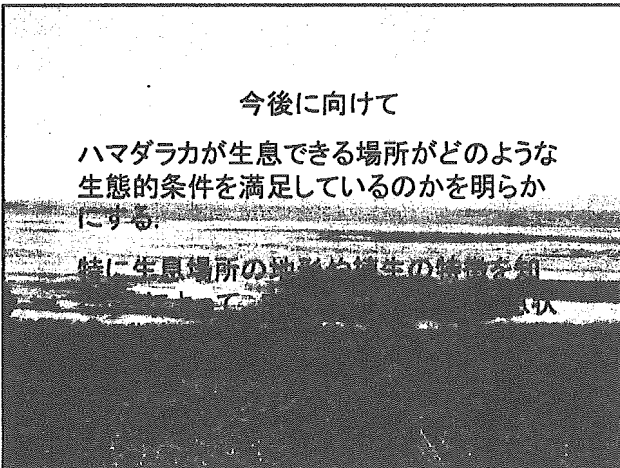
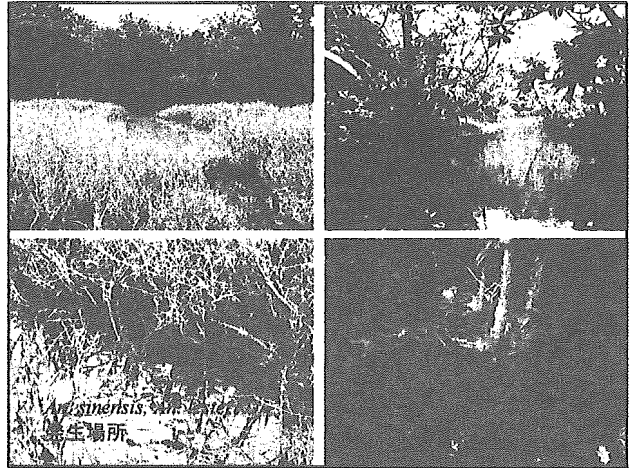
野底・浦底地域での調査結果

人囀採集

<i>An. minimus</i>	310
<i>Cx. sitiens</i>	142
<i>Ma. uniformis</i>	89
<i>Ae. vexans</i>	82
<i>An. sinensis</i>	30
<i>An. lesteri</i>	24
<i>Ar. subalbatus</i>	23
<i>Cx. pseudovishnui</i>	15
<i>Ae. albopictus</i>	9
<i>Cx. tritaeniorhynchus</i>	8
<i>Ae. riversi</i>	6
<i>Cq. crasipes</i>	4
<i>Cx. vishnui</i>	4
<i>Cx. tritaeniorhynchus</i>	3
<i>Cx. hayashii ryukyuanus</i>	1
<i>Cx. quinquefasciatus</i>	1
<i>Oc. japonicus</i>	1

ドライアイス
トラップ採集

<i>Cx. sitiens</i>	855
<i>Cq. crasipes</i>	449
<i>Ae. albopictus</i>	153
<i>An. minimus</i>	153
<i>Ae. riversi</i>	84
<i>Cx. pseudovishnui</i>	82
<i>Cx. tritaeniorhynchus</i>	86
<i>Cx. nigropunctatus</i>	56
<i>Cx. (Culicomyia) nigropunctatus</i>	49
<i>Cx. bitaeniorhynchus</i>	52
<i>Ur. annandalei</i>	45
<i>Ur. macfarlanei</i>	31
<i>Ur. ohanae</i>	29
<i>Or. anopheloides</i>	24
<i>Ma. uniformis</i>	23
<i>Ar. subalbatus</i>	20
<i>Ur. yaeyamana</i>	19
<i>Mi. elegans</i>	11
<i>Cx. okinawae</i>	6
<i>Cx. (Culicomyia) ryukyensis</i>	4
<i>Mi. luzonensis</i>	4
<i>Ur. lateralis</i>	4
<i>An. sinensis</i>	3
<i>Cx. quinquefasciatus</i>	2
<i>Cx. ryukyensis</i>	2
<i>Ur. jacksoni</i>	2
<i>Ur. novobscura</i>	2
<i>Ae. flavopictus</i>	1
<i>Tr. Bambusa</i>	1



成田国際空港におけるマラリア等の 昆虫媒介性感染症の監視状況

アジアで流行している感染症のわが国への
侵入監視の強化に関する研究
Tokyo, January 31-February 1, 2006

Michio Haseyama

Assistant director for Sanitation Division
Narita Airport Quarantine Station
Ministry of Health, Labor and Welfare

検疫感染症と法律

検疫法 No.145 (2003)

この法律は、国内に常在しない感染症の病原体が船舶又は航空機を介して国内に侵入することを防止するとともに、船舶又は航空機に関してその他の感染症の予防に必要な措置を講ずることを目的とする。

この法律において「検疫感染症」とは、次に掲げる感染症をいう。

1 エボラ出血熱、クリミア・コンゴ出血熱、SARS、痘そう、ペスト、マールブルグ病、ラッサ熱

2 コレラ 3 黄熱

政令で定めるもの

マラリア、デング熱、ウエストナイル熱、腎症候性出血熱、日本脳炎、ハンタウイルス肺症候群

2

ベクターサーベイランスと法律

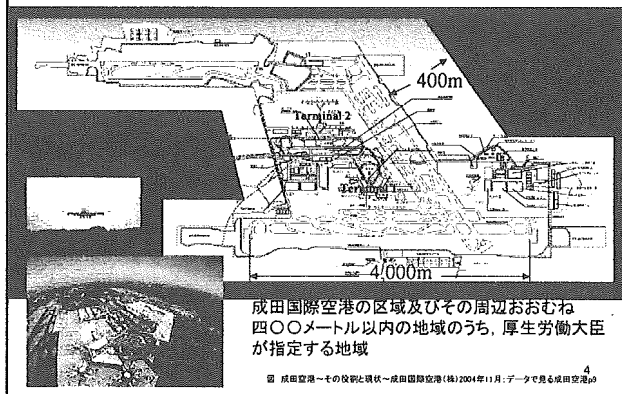
検疫法第二十七条
(検疫所長の行う調査及び衛生措置)

検疫所長は、検疫感染症…の病原体を媒介する虫類の有無その他…当該…飛行場の衛生状態を明らかにするため…政令で定める区域内に限り…航空機…当該区域内…施設、建築物その他の場所について…虫類の調査を行い、又は検疫官をしてこれを行わせることができる。

2 検疫所長は、前項に規定する感染症が流行し、…おそれがあると認めるときは、…虫類の駆除を行い、又は検疫官その他適当と認める者をしてこれを行わせることができる。

3

成田国際空港の調査対象区域(政令区域)



4

ガイドラインによるサーベイランス

食安検発第0803001号 平成17年8月3日
「港湾区域等衛生管理業務の手引きについて」

港湾衛生管理ガイドライン

○港湾衛生対策

I ねずみ族調査マニュアル

(ペスト、ラッサ熱、腎症候性出血熱、ハンタウイルス肺症候群)

II ねずみ族寄生虫調査マニュアル(ペスト)

III 蚊族調査マニュアル

(黄熱、マラリア、デング熱、ウエストナイル熱、日本脳炎)

IV

○環境衛生対策(コレラ対策)

V 海水調査マニュアル

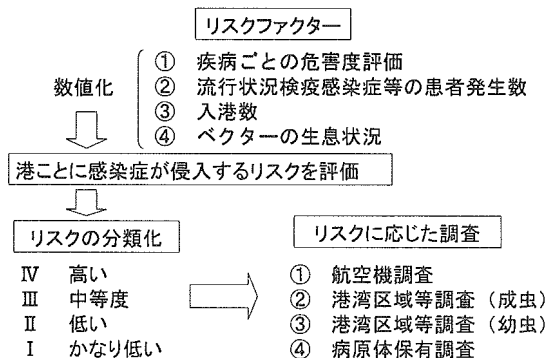
VI 飲料水調査マニュアル

VII 機内食調査マニュアル

VIII 汚水汚物調査マニュアル

5

リスクアセスメントに基づくベクターサーベイランス



6