Malaria drug resistance

Drug resistant falciparum malaria is a major threat to mankind and the Greater Mekong Subregion is a global epicenter, whence many drug resistant parasite strains are transferred to other parts of the world. Drug resistance thus is a top priority for the region and drug policy is a major area for collaboration among the countries concerned. .

Resistance of Plasmodium falciparum to anti-malarial drugs has long been known and is extensively recorded (Ejov, 1999; Gay *et al* 1990; 1997; Harinasuta *et al*, 1990; Looareesuwan *et al*, 1998; Schapira *et al*, 1993; Thimasarn *et al*, 1998; Wernsdorfer *et al,* 1994; WHO 1997; Wilairatana *et a*l, 1998). Although chloroquine resistance was first noticed in Thailand about 1960, it took considerable time, until the mid-1970s for chloroquine resistance in the region to reach a frequency and a degree that necessitated its replacement by sulfadoxine-pyrimethamine (S-P). This combination, was replaced in 1982 by quinine-tetracycline (Thaithong *et al*, 1990), followed by a shift to mefloquine in combination with S-P (Harinasuta *et al*, 1988). In the 1990s a transition was made to qinghaosu derivatives alone or in combination.

Assessment of drug resistance can be carried out in vivo (on patients) or in vitro (in the laboratory): both can provide useful information. Both have been used in countries in the region to give an indication of changing drug status of falciparum parasite strains circulating in various communities progressively over time. To gain an impression of the changing situation it is instructive to look at a number of reports in the region.

A recent report by Mey Bouth Denis (Denis, 1999) surveys the scene in Cambodia. One exerpt reviews the in vivo response to four drugs (artesunate, chloroquine, S-P, mefloquine) in eastern and western provinces of the country in the period 1991-97 (Figure 27). The responses were variable, while there was considerable resistance to S-P in two sites 5 years apart in time and some resistance to mefloquine, a surprising feature was the relative sensitivity to chloroquine in two sites. Further examination of response to chloroquine (Figure 28) yielded a summary map which suggests that in the four easternmost provinces chloroquine sensitive *P. falciparum* is predominant, in the six northwestern provinces chloroquine resistant *P. falciparum* is predominant and in between greater variability is found.

In Viet Nam in the period 1992-96 (Mekong Malaria Forum, 1998) there was recorded considerable in vivo resistance to both chloroquine and

S-P (Figure 29) but still a variable spectrum. Widespread sampling'in Myanmar in the period 1991-97 (MOH, Myanmar 1999) assessed in vivo responses to mefloquine, S-P and chloroquine (Figure 30). A feature was the sensitivity to mefloquine at several diverse sites in the period 1992-95 but considerable resistance to S-P. Chloroquine resistance was common but sensitive strains existed to both chloroquine and S-P.

In the period 1991-95 a series of in vitro drug resistance studies were carried out in Yunnan in sites close to the borders with Myanmar, Lao PDR (Yang *et al*, 1997) and Viet Nam (Yang *et al*, 1995). These sites were chosen to provide information for all countries concerned. The data are shown in Figure 31. There was no resistance to quinine or mefloquine, but there was high resistance to chloroquine and amodiaquine, moderate resistance to pyronaridine and some unexpected resistance to artesunate, dihydroartemisinin and arteether. This type of surveillance is of great value, looking at a large panel of drugs, but the possible resistance to the artesunate series of drugs gives cause for concern since these are now the last line drugs in the region.

Studies by the malaria program in Thailand (MOPH Thailand, 1993) showed an interesting pattern of resistance (in vivo/in vitro) to five anti-malarial drugs/drug combinations: S-P, MSP, mefloquine, chloroquine, quinine (Figure 32). In two provinces, one in the east (Trat), one in the west (Tak) there was considerable resistance to all five drugs, while in eight other sentinel points in different border provinces resistance was confined to S-P and chloroquine. The two high points arguably had more crossborder traffic at that time.

Figure 32 also shows an overview chart (MOPH Thailand, 1999) of Thai drug policy shifts over the extensive period 1965-98 and corresponding shifts in the ratio of the two main parasite species. This is a remarkable record and suggests that there may be a relationship between changing drug responses of *P.falciparum* and the balance in the community of infection with this parasite species. Perhaps this is another factor to add to interpretation the intriguing distribution pattern of parasite species noted in Figure 17.

A dramatic example of rapid spread of drug resistant parasite strains is provided by a report (Thimasarn *et al*, 1995) on itinerant gem miners working in the Pailin area in Cambodia in the period 1988-92 (Figure 33). Many miners died of clinical malaria in the Pailin gem fields, an area not under government control at that time. Others returned home via the official Borai border crossing point, largely to Trat (east) and Tak (west) provinces, carrying drug resistant malaria. There was a rapid spread of resistant

strains in both areas, as indicated by a precipitous fall in MSP (mefloquine S-P) cure rate over a short time frame in the two provinces. From Tak the resistant strains rapidly spread to Myanmar and beyond. It is rare to obtain such a population case history, it is one that serves as a reminder of how fast drug resistance can spread given large scale population movement across international or internal boundaries.

The observation that chloroquine sensivity as now being found in some areas of Cambodia is intriguing, suggesting as it does the possbility of reversion after periods of non-use. A study in Hainan corroborates this thesis. Chloroquine use was stopped in Hainan in 1979 due to high levels of resistance (Figure 34, upper graph). Subsequent monitoring has revealed a gradual decline in resistant strains to about 20% in 1997. The possibility of chloroquine making a comeback is interesting for future consideration.

Another study, in Yunnan (Figure 34, lower graph) gives cause for concern about the future: cross resistance among responses to drugs of the artesunate series. In this study (Yang *et al*, 1997) *P. falciparum* was isolated from patients with clinical resistance and clinical sensitivity, cultured in vitro, then tested for response to the several drugs shown. The in vitro responses agreed with the clinical responses and both groups were resistant to chloroquine as expected in that area of Yunnan. The artesunate resistant strains were also resistant to dihydroartemisinin and to arteether. Although artesunate resistant falciparum is still uncommon, when it arises it may carry similar responses to the other drugs in the series, so that we might eventually expect to see diminished utility of the whole qinghaosu group. Cross-resistance to pyronaridine is perhaps surprising.

The dynamics of drug resistance spread are shown versus time in Figure 35. Mefloquine was introduced about 1984 and sensitivity began to decline quite quickly at the same time that S-P sensitivity decreased precipitously. Response to quinine has declined more slowly. Overall the picture is not too encouraging. However, it is appropriate to retain a positive approach: Figure 36 summarizes current treatment regimens with combination mefloquine and artesunate in a number of sites along Thai borders MOPH Thailand, 1997). Adaptation to different dosage schedules is necessary to cope with differing sensitivities: but compliance is correspondingly more difficult at community level. This cautious optimism needs to be coupled with tighter drug policy, something that will require regional agreement.

Data sources: Malaria programs of the country health ministries and published data in references quoted.

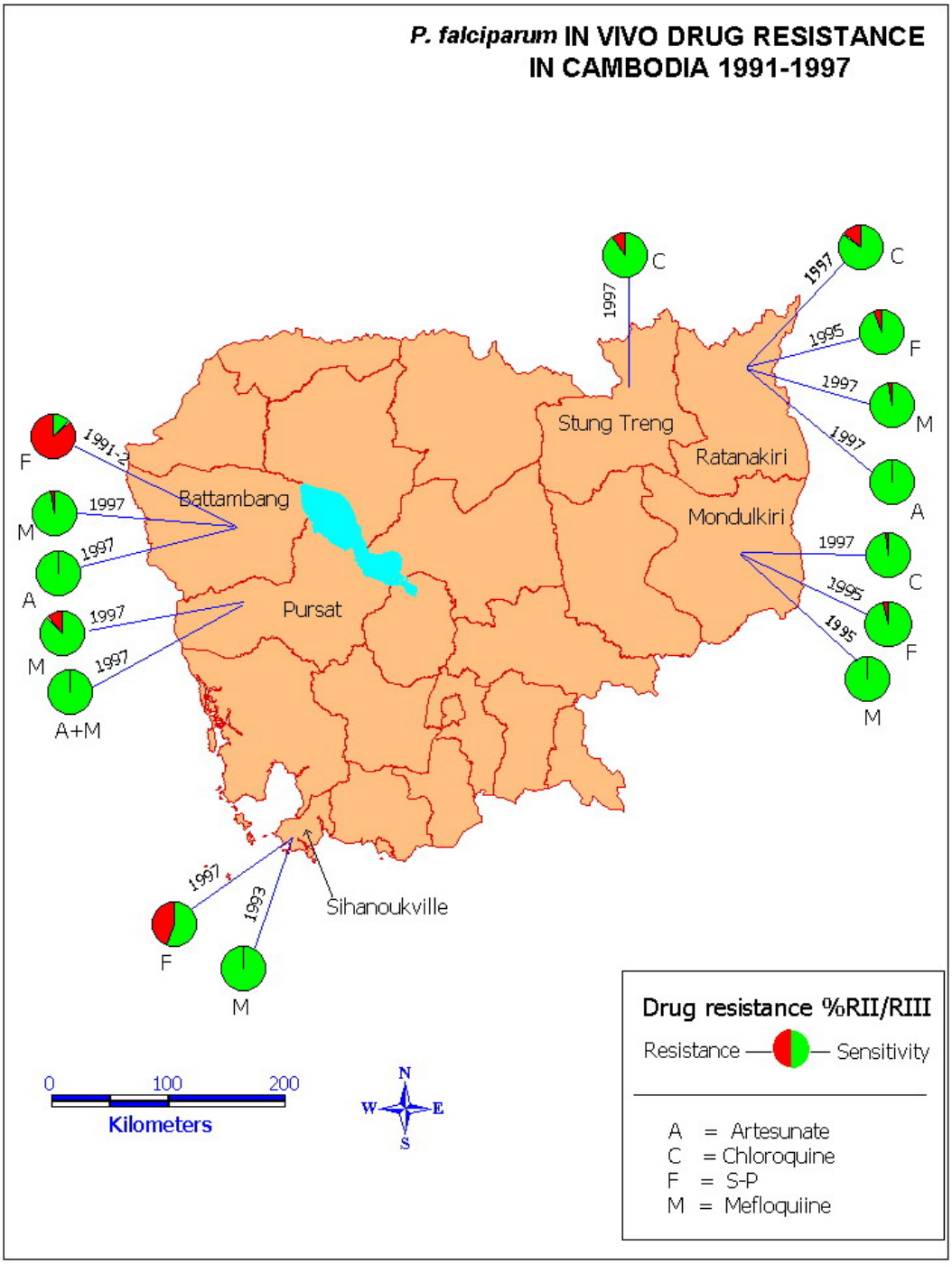

P. falciparum IN VIVO DRUG RESISTANCE
IN CAMBODIA 1991-1997
Stung Treng
Ratanakiri
Mondulkiri
Battambang
Pursat
Sihanoukville
C
1997
F
1995
M
A
1991-2
A+M
1993
0
100
200
Kilometers
N
W
E
S
Drug resistance %RII/RIII
Resistance
Sensitivity
A = Artesunate
C = Chloroquine
F = S-P
M = Mefloquiine

FIGURE 27.

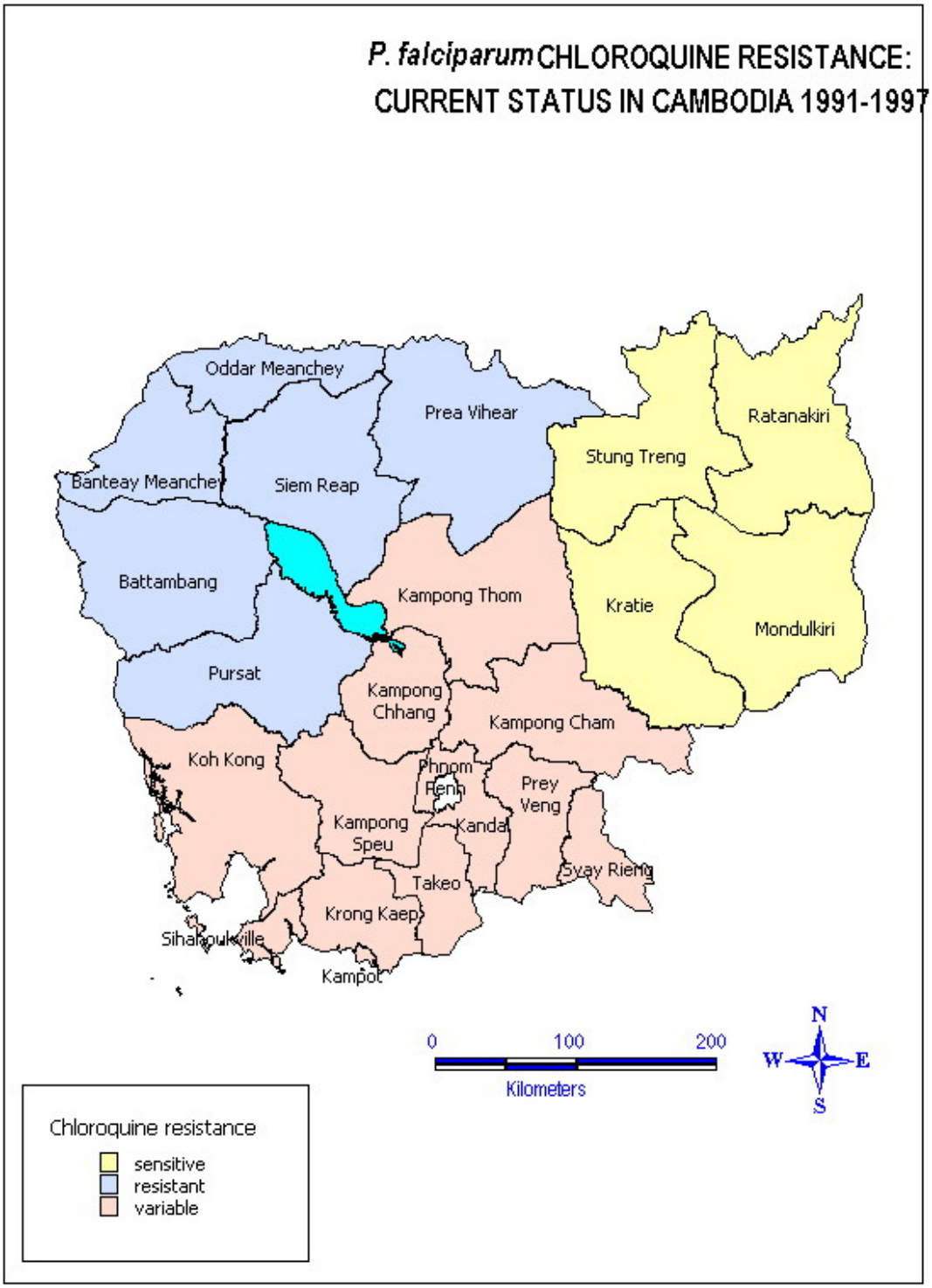

P. falciparum CHLOROQUINE RESISTANCE:
CURRENT STATUS IN CAMBODIA 1991-1997
Oddar Meanchey
Prea Vihear
Ratanakiri
Stung Treng
Banteay Meanchey
Siem Reap
Battambang
Kampong Thom
Kratie
Mondulkiri
Pursat
Kampong Chhang
Kampong Cham
Koh Kong
Phnom Penh
Prey Veng
Kampong Speu
Kandal
Svay Rieng
Takeo
Krong Kaep
Sihanoukville
Kampot
0
100
200
Kilometers
N
W
E
S
Chloroquine resistance
sensitive
resistant
variable

Figure 28.

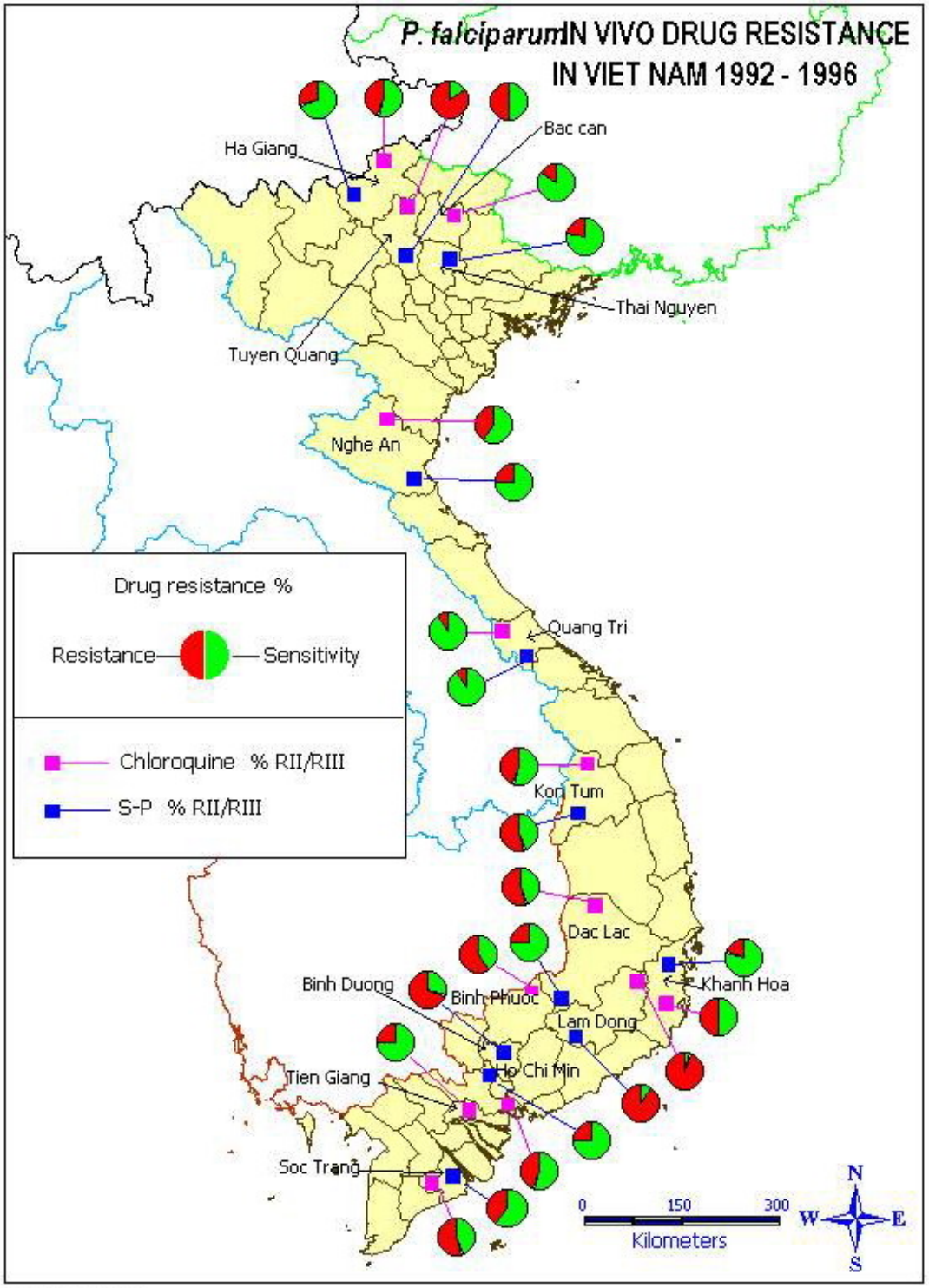

P. falciparum IN VIVO DRUG RESISTANCE
IN VIET NAM 1992 - 1996
Ha Giang
Bac can
Thai Nguyen
Tuyen Quang
Nghe An
Drug resistance %
Resistance
Sensitivity
Chloroquine % RII/RIII
S-P % RII/RIII
Quang Tri
Kon Tum
Dac Lac
Binh Duong
Binh Phuoc
Khanh Hoa
Lam Dong
Ho Chi Min
Tien Giang
Soc Trang
0
150
300
Kilometers
N
W
E
S

FIGURE 29.

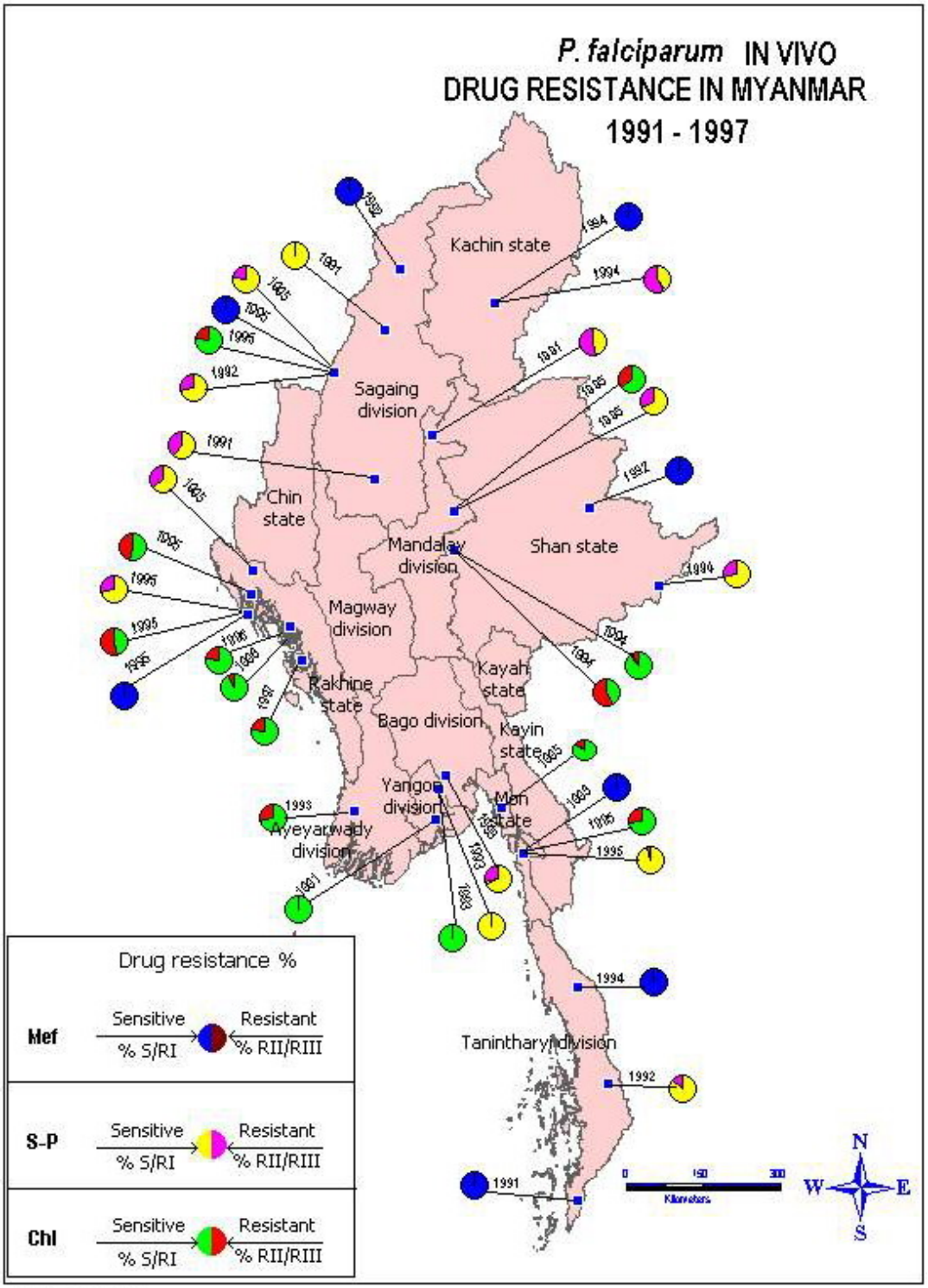

P. falciparum IN VIVO
DRUG RESISTANCE IN MYANMAR
1991 - 1997
Kachin state
Sagaing division
Chin state
Mandalay division
Shan state
Magway division
Rakhine state
Kayah state
Bago division
Kayin state
Yangon division
Mon state
Ayeyarwady division
Tanintharyi division
Drug resistance %
Mef
Sensitive
% S/RI
Resistant
% RII/RIII
S-P
Sensitive
% S/RI
Resistant
% RII/RIII
Chl
Sensitive
% S/RI
Resistant
% RII/RIII
0
150
300
Kilometers
N
W
E
S

FIGURE 30.

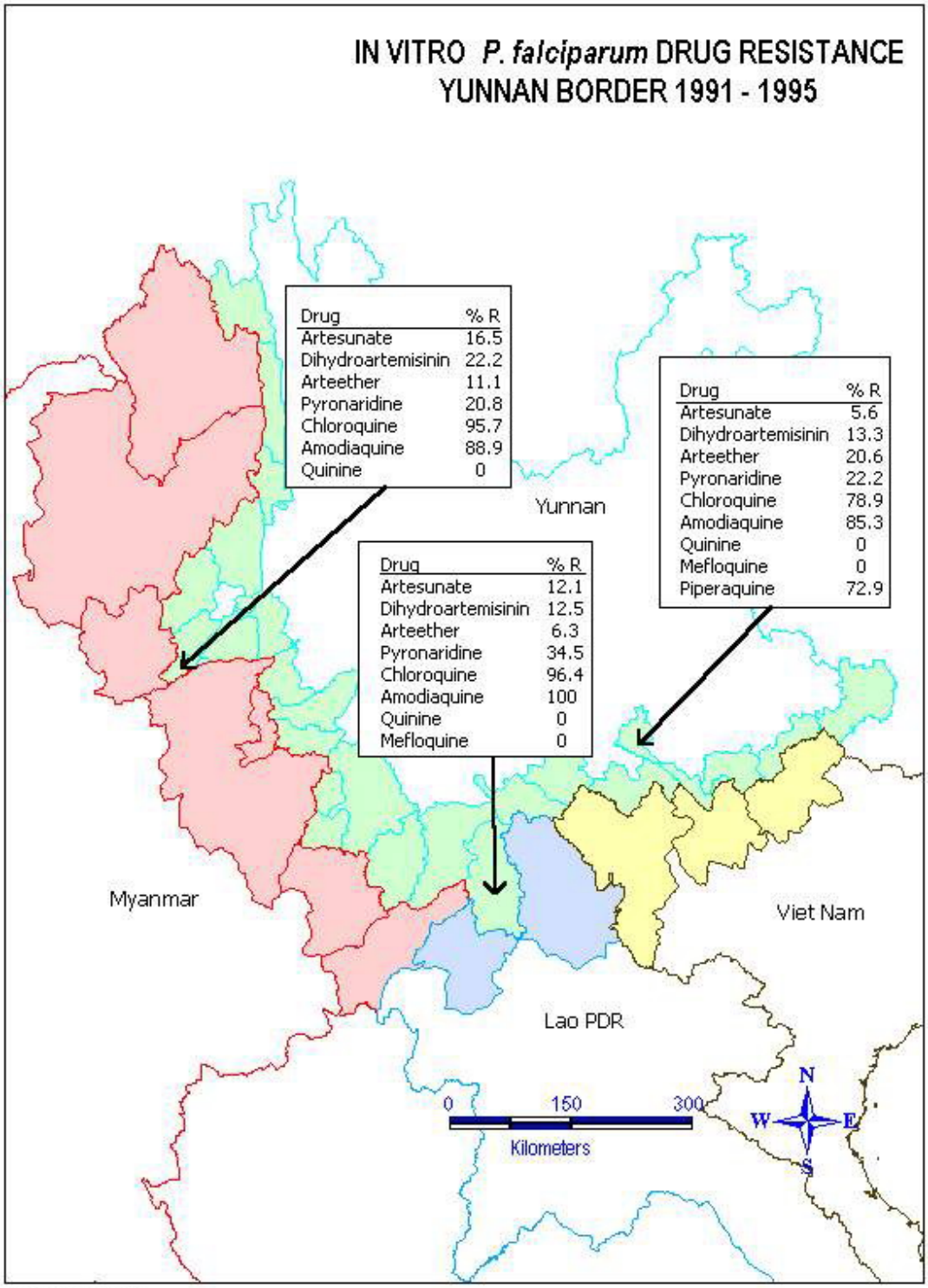

IN VITRO P. falciparum DRUG RESISTANCE
YUNNAN BORDER 1991 - 1995
Drug % R
Artesunate 16.5
Dihydroartemisinin 22.2
Arteether 11.1
Pyronaridine 20.8
Chloroquine 95.7
Amodiaquine 88.9
Quinine 0
Drug % R
Artesunate 5.6
Dihydroartemisinin 13.3
Arteether 20.6
Pyronaridine 22.2
Chloroquine 78.9
Amodiaquine 85.3
Quinine 0
Mefloquine 0
Piperaquine 72.9
Drug % R
Artesunate 12.1
Dihydroartemisinin 12.5
Arteether 6.3
Pyronaridine 34.5
Chloroquine 96.4
Amodiaquine 100
Quinine 0
Mefloquine 0
Yunnan
Myanmar
Viet Nam
Lao PDR
0
150
300
Kilometers
N
W
E
S

FIGURE 31.

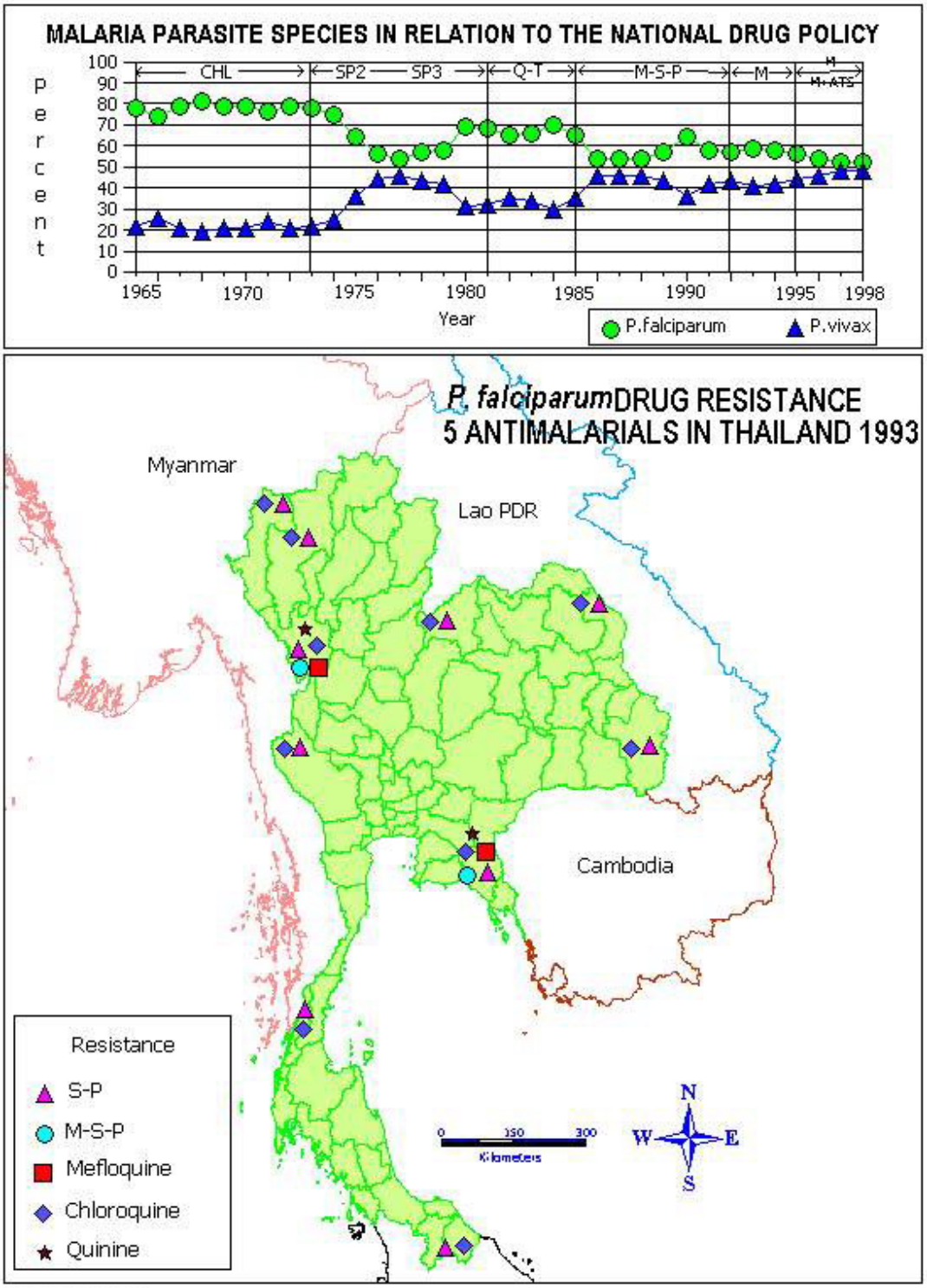

MALARIA PARASITE SPECIES IN RELATION TO THE NATIONAL DRUG POLICY
Percent
100
90
80
70
60
50
40
30
20
10
0
CHL
SP2
SP3
Q-T
M-S-P
M
M+ATS
1965
1970
1975
1980
1985
1990
1995
1998
Year
P.falciparum
P.vivax
P. falciparum DRUG RESISTANCE
5 ANTIMALARIALS IN THAILAND 1993
Myanmar
Lao PDR
Cambodia
Resistance
S-P
M-S-P
Mefloquine
Chloroquine
Quinine
0
150
300
Kilometers
N
W
E
S

FIGURE 32.

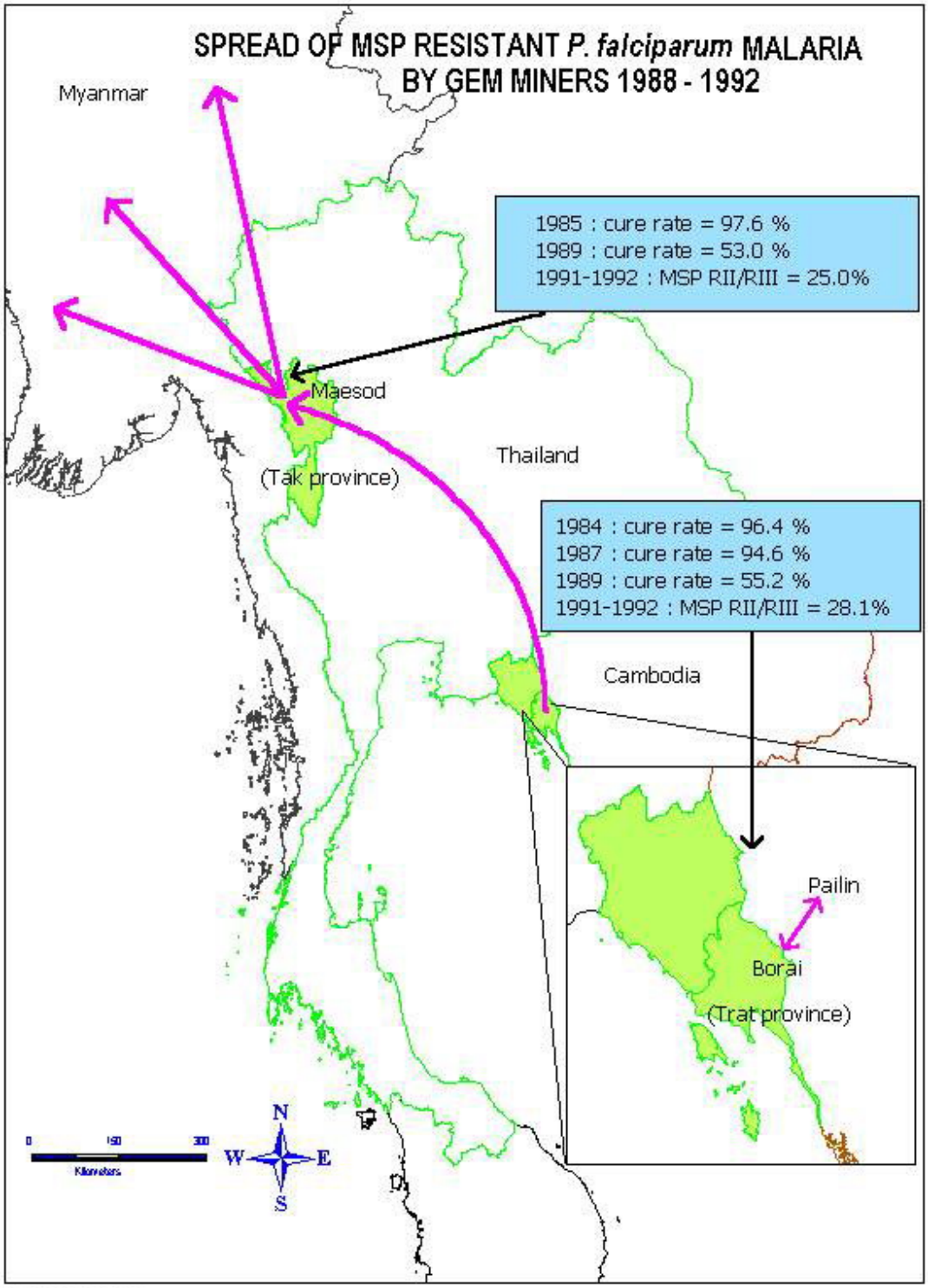
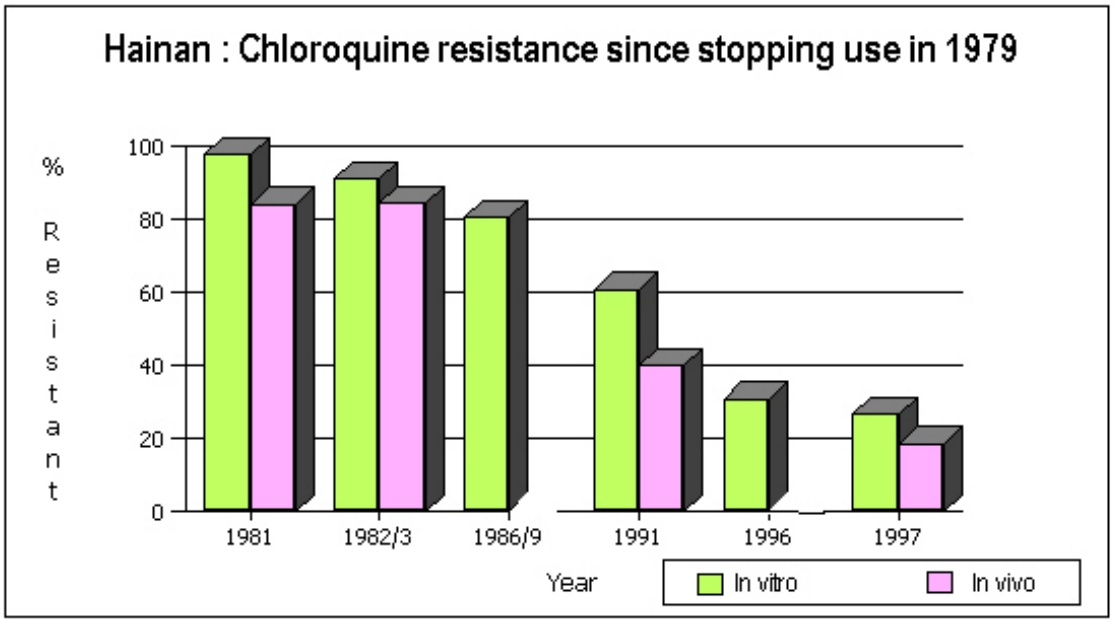
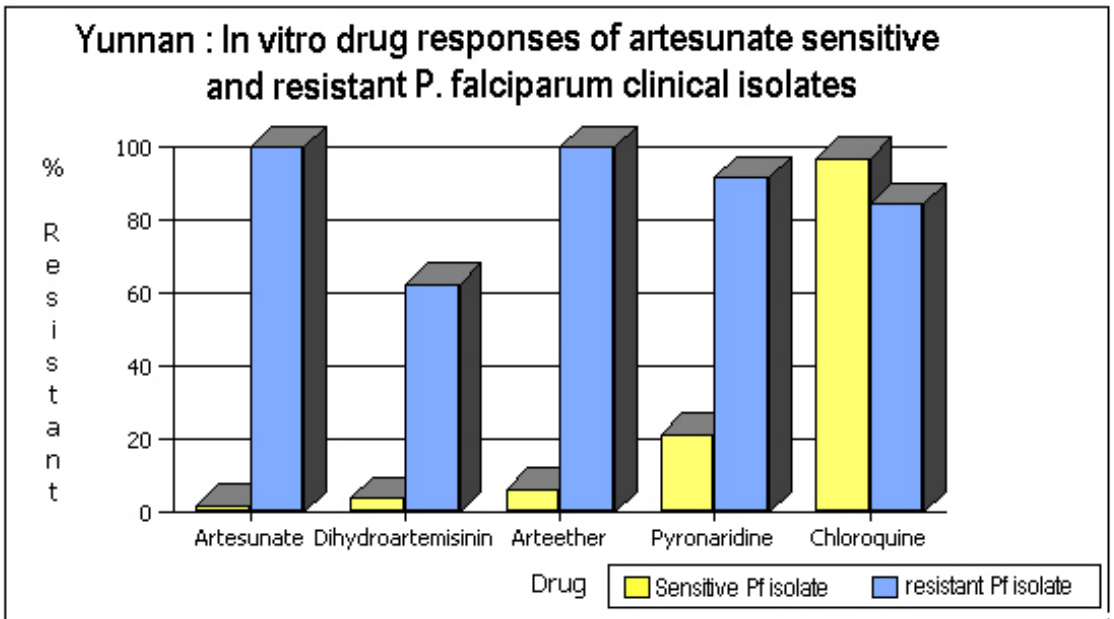

SPREAD OF MSP RESISTANT P. falciparum MALARIA
BY GEM MINERS 1988 - 1992
Myanmar
1985 : cure rate = 97.6 %
1989 : cure rate = 53.0 %
1991-1992 : MSP RII/RIII = 25.0%
Maesod
(Tak province)
Thailand
1984 : cure rate = 96.4 %
1987 : cure rate = 94.6 %
1989 : cure rate = 55.2 %
1991-1992 : MSP RII/RIII = 28.1%
Cambodia
Pailin
Borai
(Trat province)
N
W
E
S

FIGURE 33.





Clinical resistance to artesunate is rare but does occur. Isolates cultured from resistant and sensitive cases show resistance and sensitivity in vitro respectively. There is also cross resistance to other drugs. Both groups of isolates were resistant to chloroquine as expected in the area.

Figure 34. Unexpected drug resistance patterns

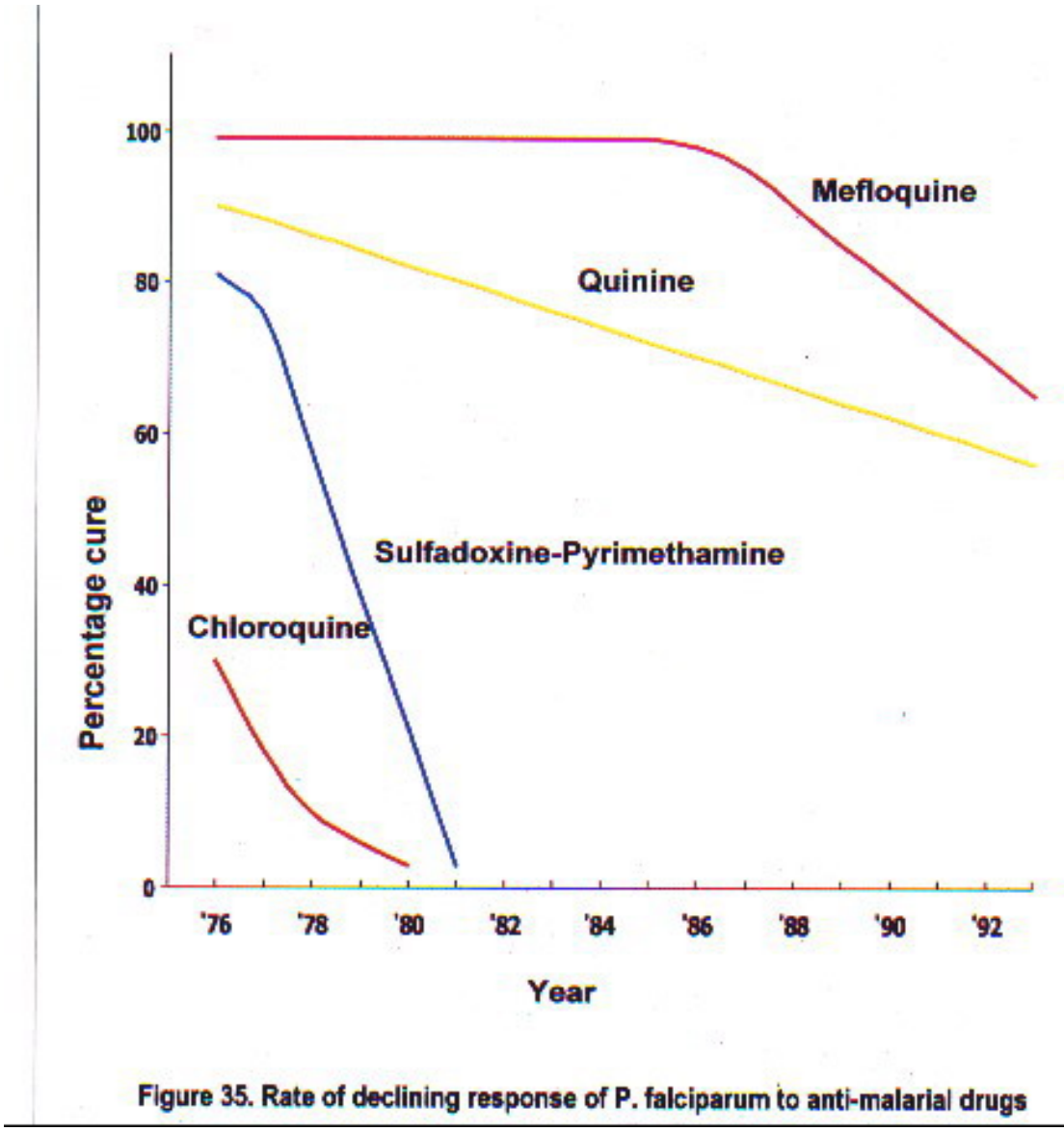


Figure 35. Rate of declining response of P. falciparum to anti-malarial drugs

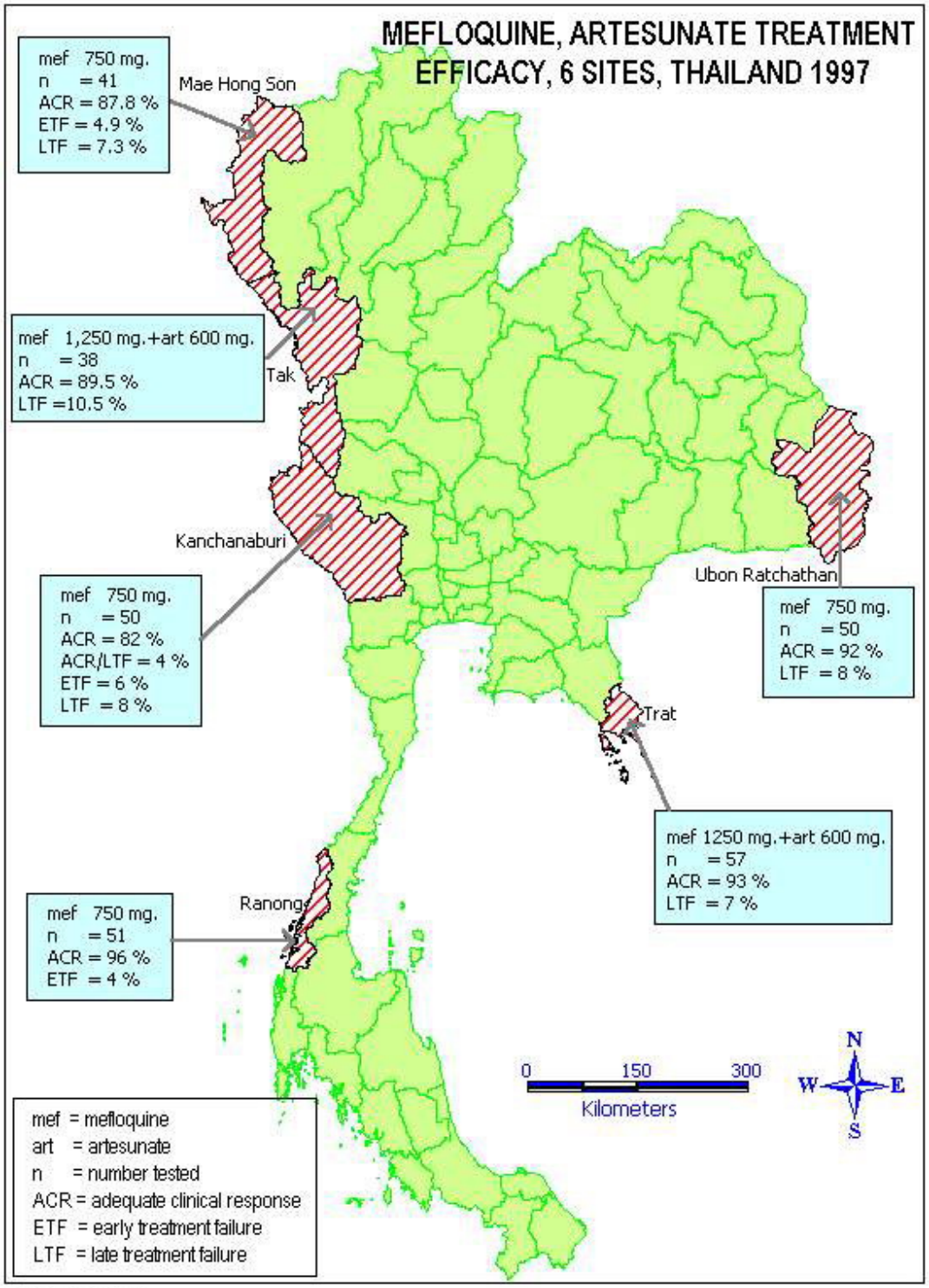

MEFLOQUINE, ARTESUNATE TREATMENT EFFICACY, 6 SITES, THAILAND 1997
mef 750 mg.
n = 41
ACR = 87.8 %
ETF = 4.9 %
LTF = 7.3 %
Mae Hong Son
mef 1,250 mg.+art 600 mg.
n = 38
ACR = 89.5 %
LTF =10.5 %
Tak
Kanchanaburi
mef 750 mg.
n = 50
ACR = 82 %
ACR/LTF = 4 %
ETF = 6 %
LTF = 8 %
Ubon Ratchathan
mef 750 mg.
n = 50
ACR = 92 %
LTF = 8 %
Trat
mef 1250 mg.+art 600 mg.
n = 57
ACR = 93 %
LTF = 7 %
Ranong
mef 750 mg.
n = 51
ACR = 96 %
ETF = 4 %
0
150
300
Kilometers
N
W
E
S
mef = mefloquine
art = artesunate
n = number tested
ACR = adequate clinical response
ETF = early treatment failure
LTF = late treatment failure

FIGURE 36.