Antimalarial drug efficacy and resistance

Threat and rapid decline in response rate to antimalarial drugs

Even a casual glance at the global malaria map produced by the World Health Organization gives cause for concern at the extent of spread of *P. falciparum* resistance to well-tried antimalarial drugs (chloroquine, sulfadoxine-pyrimethamine) and the specter of further spread of multidrug resistant parasite strains from their current enclaves in Southeast Asia and, to a lesser extent, South America (Figure 25).

It is of particular concern in the Mekong region of Southeast Asia because this is the global epicenter of drug resistance. Prevalence of parasite strains resistant to one drug provide the rationale for introduction of new drugs, to which resistance then develops, so to establish a vicious cycle. At the same time this cycle stimulates clinical trials of new candidate drugs and drug combinations in the region, *i.e.* the Mekong region acts in effect as a global monitoring system as well as a local one.

Thus this is the area of the world where the problem is most acute and where the expertise for tackling the problem has best been developed. Some records go back over many years. In this context, Figure 26 demonstrates graphically the time curves for declining response to several drugs and drug combinations based on the results of clinical trials carried out at the Hospital for Tropical Diseases in Bangkok with patients drawn from border provinces of Thailand. The differing shapes of the curves for declining efficacy to these drugs raises interesting questions concerning mechanisms of resistance.

On the basis of such data, for example, the use of chloroquine (CQ) and sulfadoxine-pyrimethamine (S-P) has long ago been discontinued in the respective areas although they are still in use in some other parts of the region.

It became evident in the presentation of drug resistance data in the preceding monograph (Kidson *et al*, 1999), that national quantitative records of efficacy/resistance are not easy to interpret, in part because of the limited systematic approach to measurement and of scattered geographical sites employed. To improve the technical capacity in this regard a decision was made by RBM-Mekong to identify 36 sentinel sites for regular assessment of drug efficacy in the region, so to create an ongoing comparative record system.

These sentinel sites are depicted in Figure 27. The minimum package of standard monitoring methods at sentinel sites has been defined as therapeutic efficacy testsing of

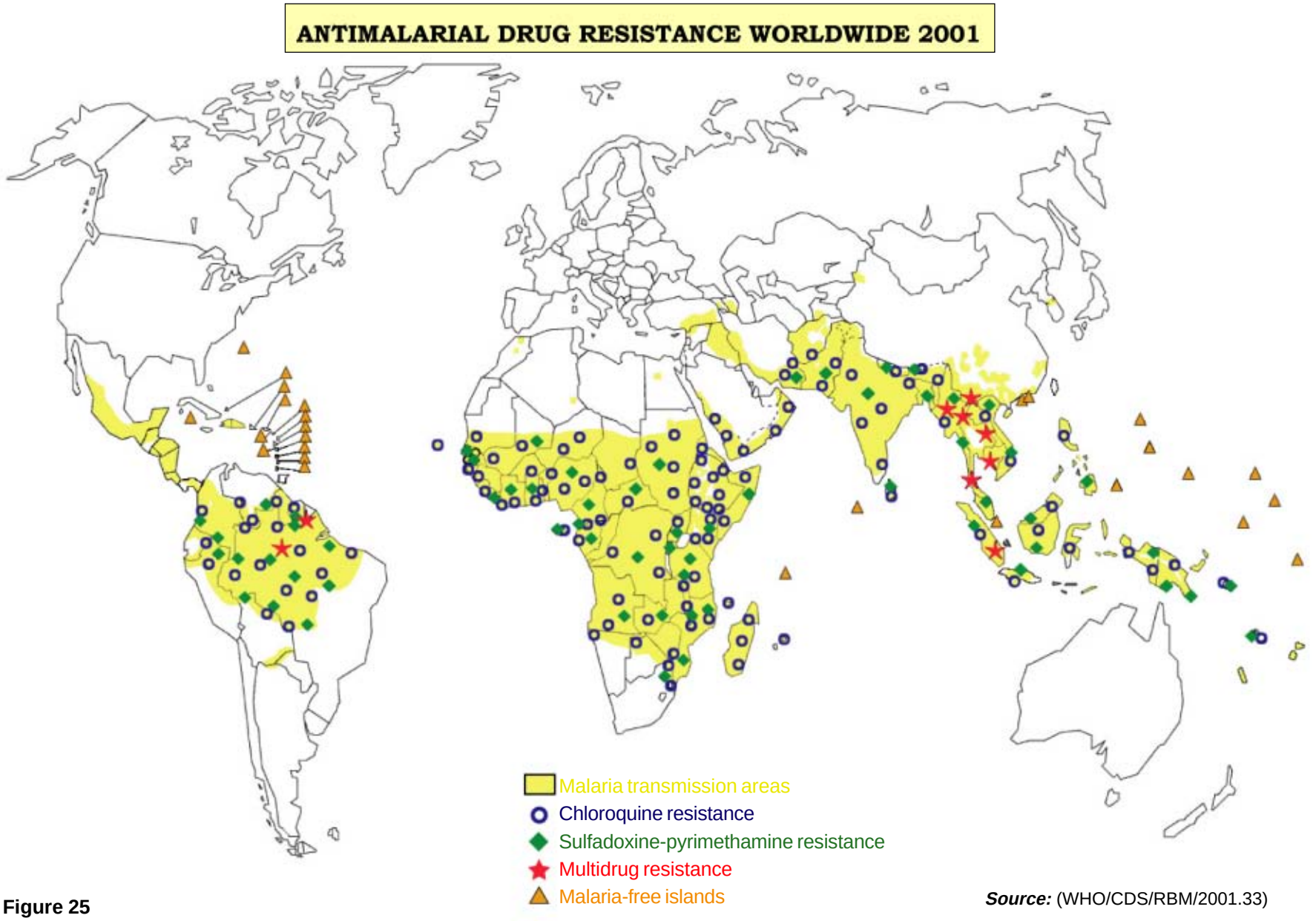
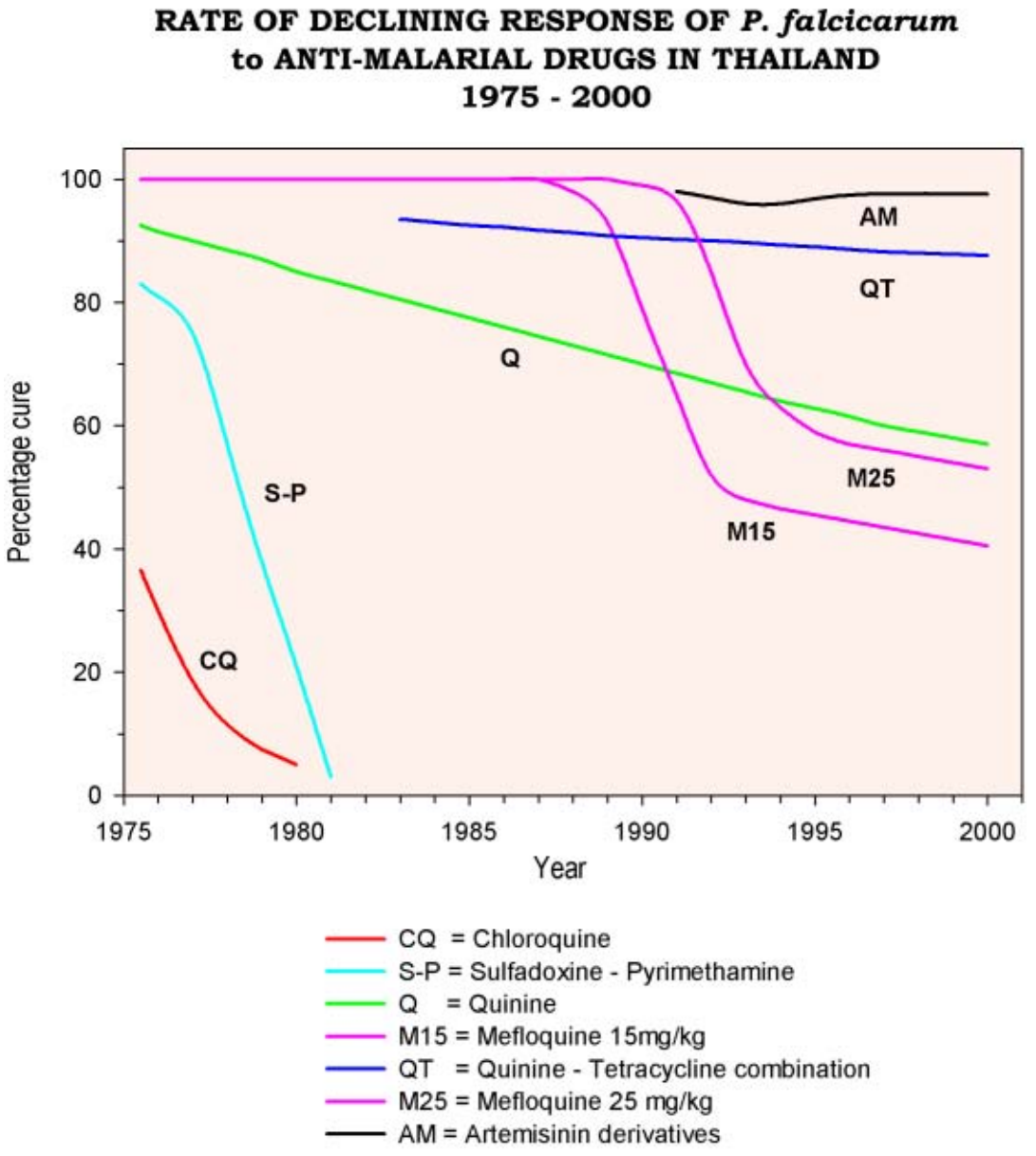


Figure 25

Source: (WHO/CDS/RBM/2001.33)



Source: Bangkok Hospital for Tropical Diseases, Faculty of Tropical Medicine.

Figure 26

the first-line and second-line treatments at least once every two years, based on the global standardized protocol (WHO, 2001). Post-treatment follow-up has been implemented in Thailand as a routine surveillance measure on days 7, 14, 21 and 28. Approximately 60% of all patients are checked on days 7 and 28, an effective measure for the early detection of treatment failure.

This initiative will yield important information on mechanisms of drug resistance and the efficacy of new antimalarial drugs. Thus far not all the sites have yet been optimally utilized, so that mapped data by country in some instances is mixed in origin, but a start has been made on the systematic record system.

The situation of drug resistance of *P. falciparum* in Mekong countries

Figure 28 looks at response to chloroquine in the period1994-2000 in Cambodia, Lao PDR, Myanmar and Viet Nam; each pie chart represents one site where evaluation of drug efficacy/resistance was assessed at a time within the stated period. Thailand no longer uses chloroquine; in China/Yunnan, the incidence of *P.falciparum* is very low and thus the imperative for frequent monitoring of resistance to chloroquine on a broad scale is not so high. Although there is generally high resistance in the sites assessed, some areas report a certain degree of efficacy. This is interesting in view of the continuing use of chloroquine as drug of first choice in some communities, in part because of the easy availability and in part because of its low cost.

In this context it is worth recalling the record in Figure 34 in the previous Mekong Malaria monograph (Kidson *et al*, 1999) that in the island province of Hainan in China the cessation of chloroquine use over many years led to a dramatic fall off of chloroquine resistance. Where chloroquine is still used for treatment of *P.vivax* in a mixed species environment such reversal of efficacy pattern would seem to be less dramatic.

Figure 29 shows a somewhat similar picture for response to sulfadoxine-pyrimethamine (S-P). Perhaps the surprising finding is that although CQ and S-P resistance took these drugs out of the Thai malaria program already quite some years ago, they still exhibit some degree of effectiveness in a substantial portion of patients in some other national malaria programs. Efficacy to mefloquine (Figure 30) is still satisfactory in the majority of areas but foci of resistance to it along parts of the Myanmar-Thailand and Cambodia borders. In those areas where combined treatment with artesunate and mefloquine is currently used for falciparum malaria the results are satisfactory.

Individual country maps record antimalarial drug efficacy reported from some of the designated sentinel sites and from some other sites in each country. Drug efficacy is expressed in terms of % adequate clinical response (ACR) to single drugs and / or drug combinations involving artemisinin derivatives.

Cambodia (Figure 31a): Efficacy to mefloquine in combination with artesunate is high on the eastern Cambodia/Viet Nam border compared to the western Cambodia/Thai border in the year 2002; which may in part at least reflect the high internal migration of


SENTINEL SITES FOR ANTIMALARIAL DRUG TESTING
IN THE MEKONG REGION
Yunnan
Bamaw
Ruili
Tamu
Myanmar
Mengla
Lao Cai
Viet Nam
Mauntaw
Tarchilake
Luangnamtha
Houphan
Lao PDR
Mae Hong Son
Xayabury
Khammuane
Quang Tri
Myawaddy
Tak
Thailand
Savannkhet
Ubon Ratchathani
Champasack
Kanchanaburi
Sa Kaeo
Oddar Meanchey
Ratchaburi
Ratanakiri
Prea Vihear
Chantaburi
Battambang
Mondulkiri
Dak Lak
Trat
Kratie
Pursat
Cambodia
Khanh Hoa
Binh Phuoc
Koh Kong
Kawthaung
Ranong
0
250
500
Kilometers
N

Figure 27

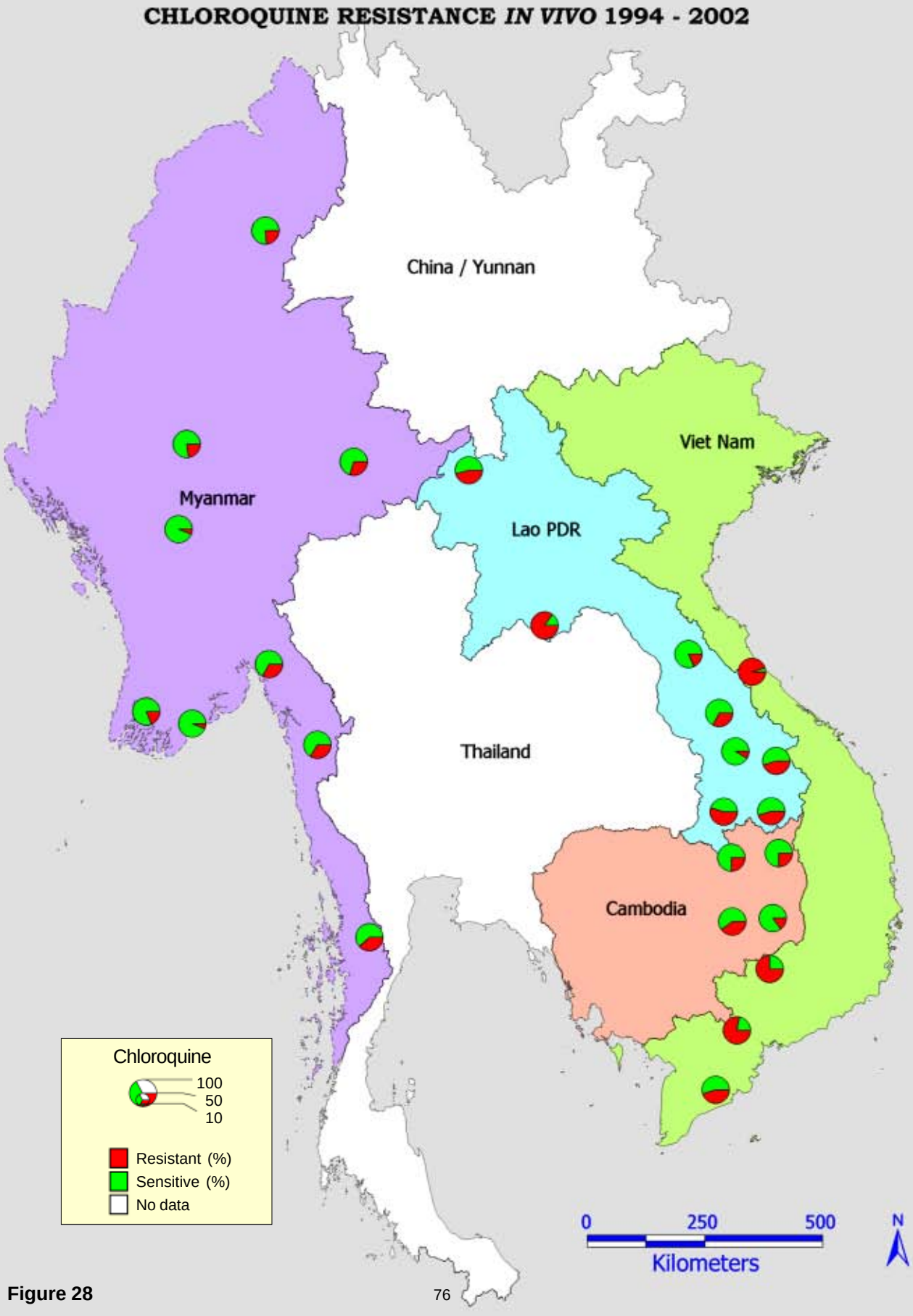

CHLOROQUINE RESISTANCE IN VIVO 1994 - 2002
China / Yunnan
Myanmar
Lao PDR
Viet Nam
Thailand
Cambodia
Chloroquine
100
50
10
Resistant (%)
Sensitive (%)
No data
0
250
500
Kilometers
N

Figure 28

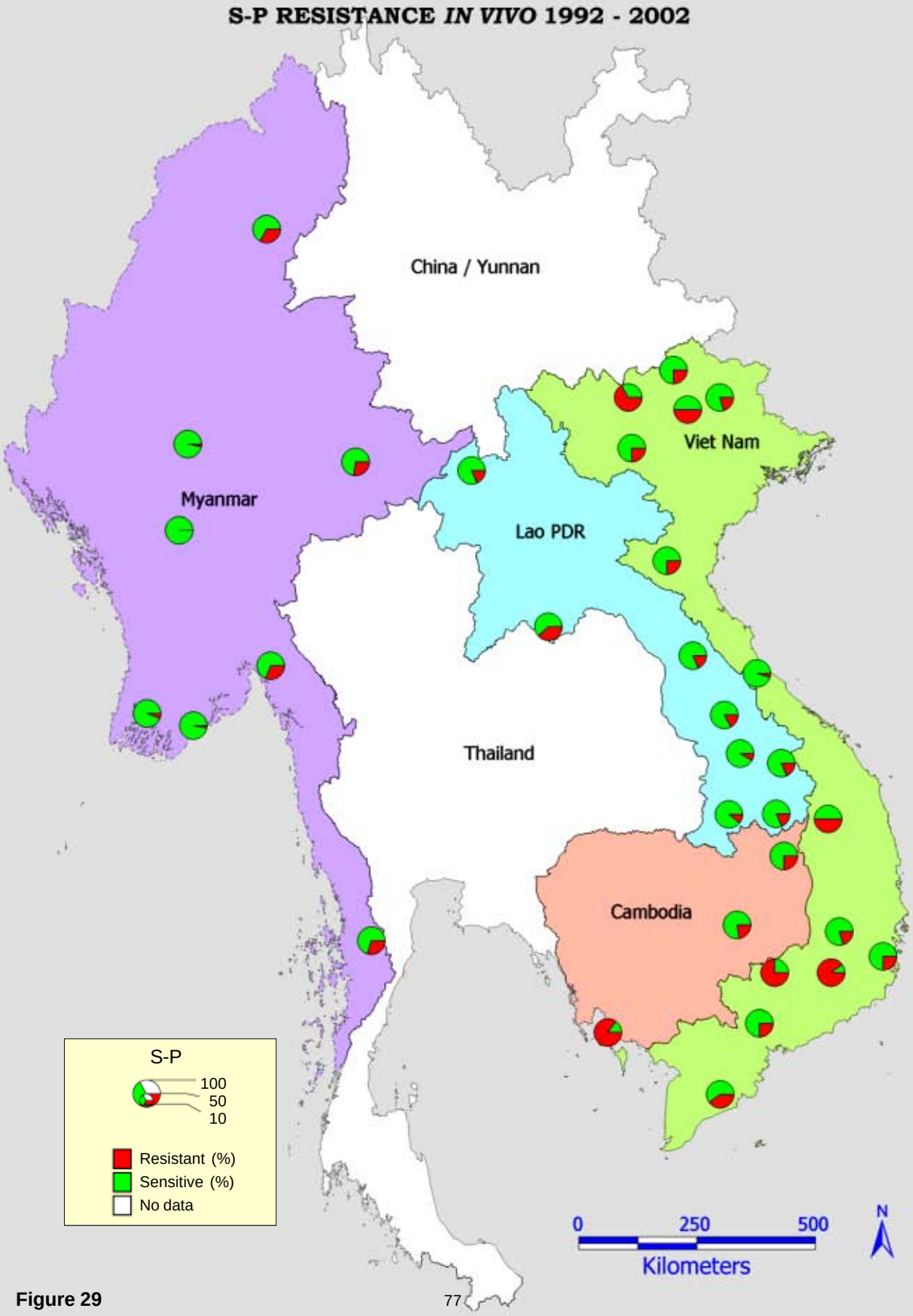

S-P RESISTANCE IN VIVO 1992 - 2002
China / Yunnan
Viet Nam
Myanmar
Lao PDR
Thailand
Cambodia
S-P
100
50
10
Resistant (%)
Sensitive (%)
No data
0
250
500
Kilometers
N

Figure 29

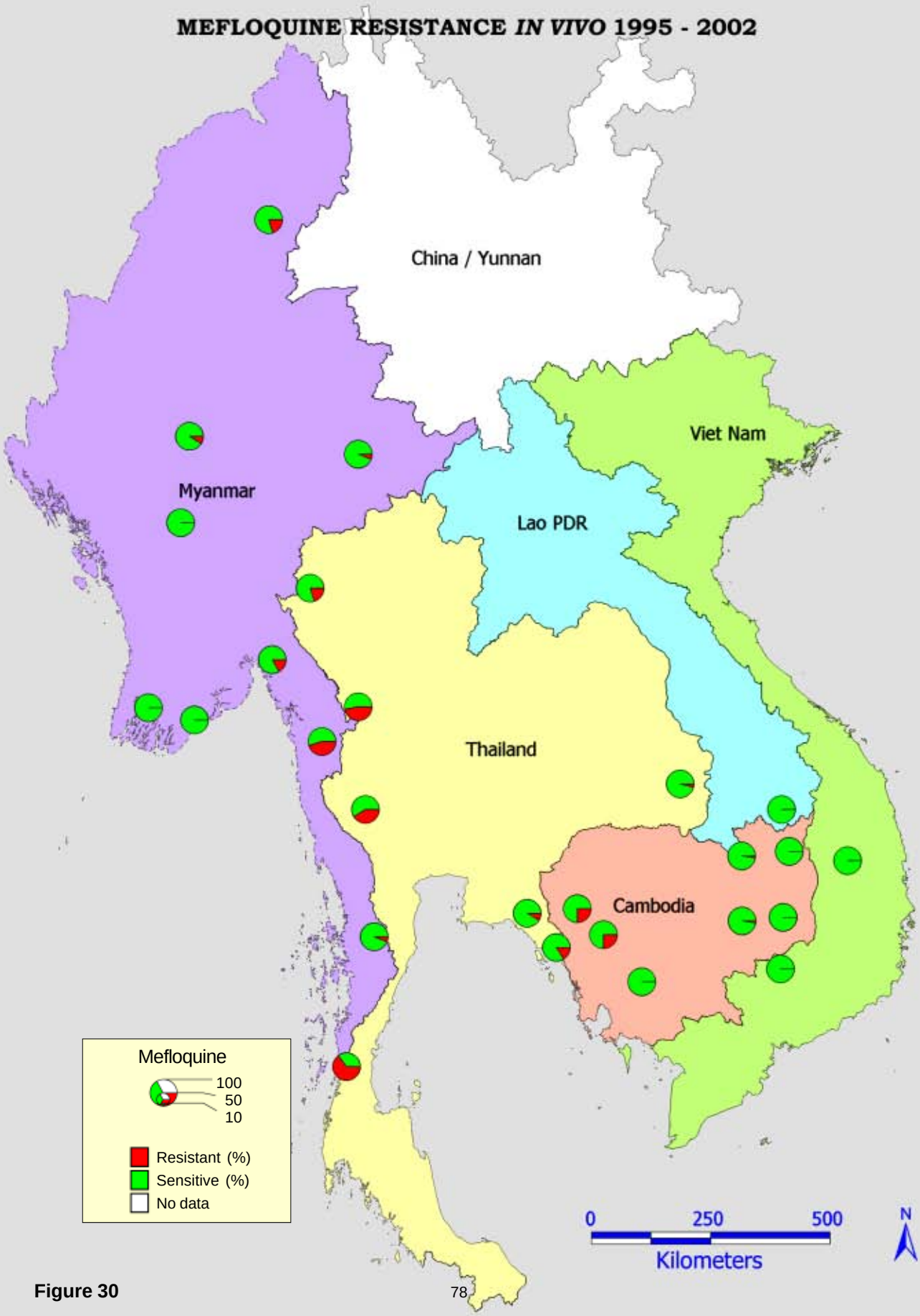

MEFLOQUINE RESISTANCE IN VIVO 1995 - 2002
China / Yunnan
Myanmar
Viet Nam
Lao PDR
Thailand
Cambodia
Mefloquine
100
50
10
Resistant (%)
Sensitive (%)
No data
0
250
500
Kilometers
N

Figure 30

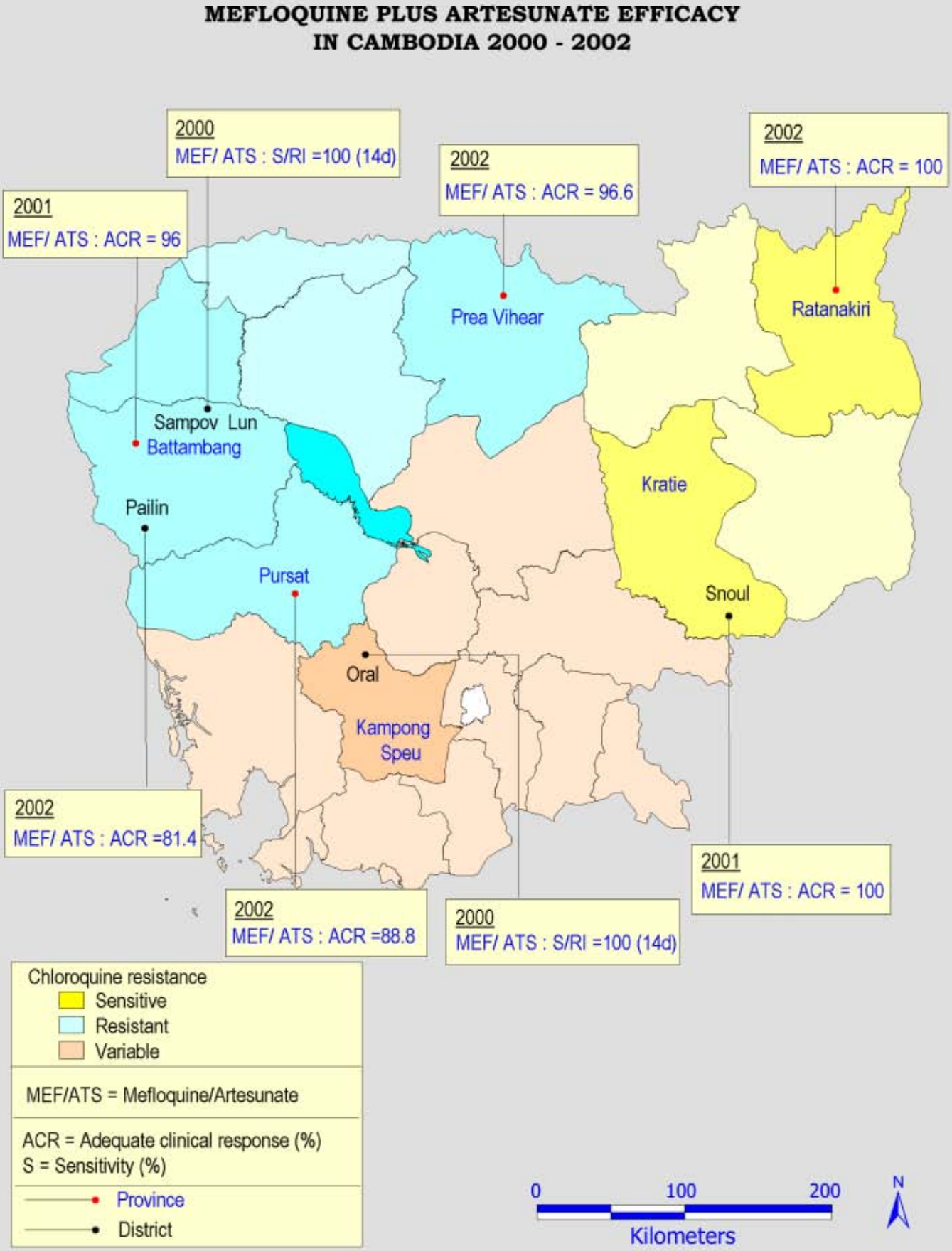

MEFLOQUINE PLUS ARTESUNATE EFFICACY
IN CAMBODIA 2000 - 2002
2000
MEF/ ATS : S/RI =100 (14d)
2001
MEF/ ATS : ACR = 96
2002
MEF/ ATS : ACR = 96.6
2002
MEF/ ATS : ACR = 100
Prea Vihear
Ratanakiri
Sampov Lun
Battambang
Pailin
Pursat
Kratie
Snoul
Oral
Kampong
Speu
2002
MEF/ ATS : ACR =81.4
2002
MEF/ ATS : ACR =88.8
2000
MEF/ ATS : S/RI =100 (14d)
2001
MEF/ ATS : ACR = 100
Chloroquine resistance
Sensitive
Resistant
Variable
MEF/ATS = Mefloquine/Artesunate
ACR = Adequate clinical response (%)
S = Sensitivity (%)
Province
District
0
100
200
Kilometers
N

Figure 31a

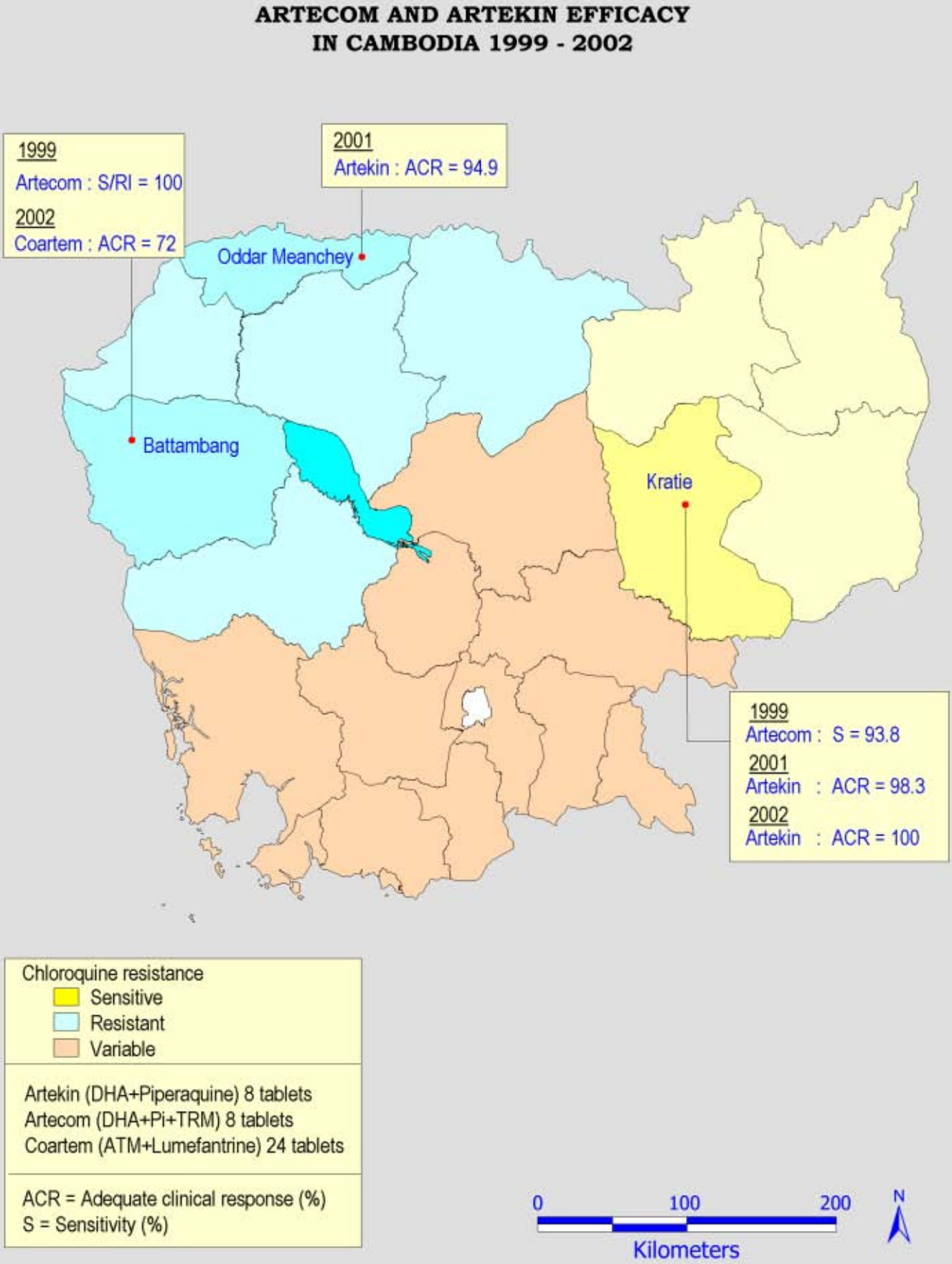

ARTECOM AND ARTEKIN EFFICACY
IN CAMBODIA 1999 - 2002
1999
Artecom : S/RI = 100
2002
Coartem : ACR = 72
2001
Artekin : ACR = 94.9
Oddar Meanchey
Battambang
Kratie
1999
Artecom : S = 93.8
2001
Artekin : ACR = 98.3
2002
Artekin : ACR = 100
Chloroquine resistance
Sensitive
Resistant
Variable
Artekin (DHA+Piperaquine) 8 tablets
Artecom (DHA+Pi+TRM) 8 tablets
Coartem (ATM+Lumefantrine) 24 tablets
ACR = Adequate clinical response (%)
S = Sensitivity (%)
0
100
200
Kilometers
N

Figure 31b

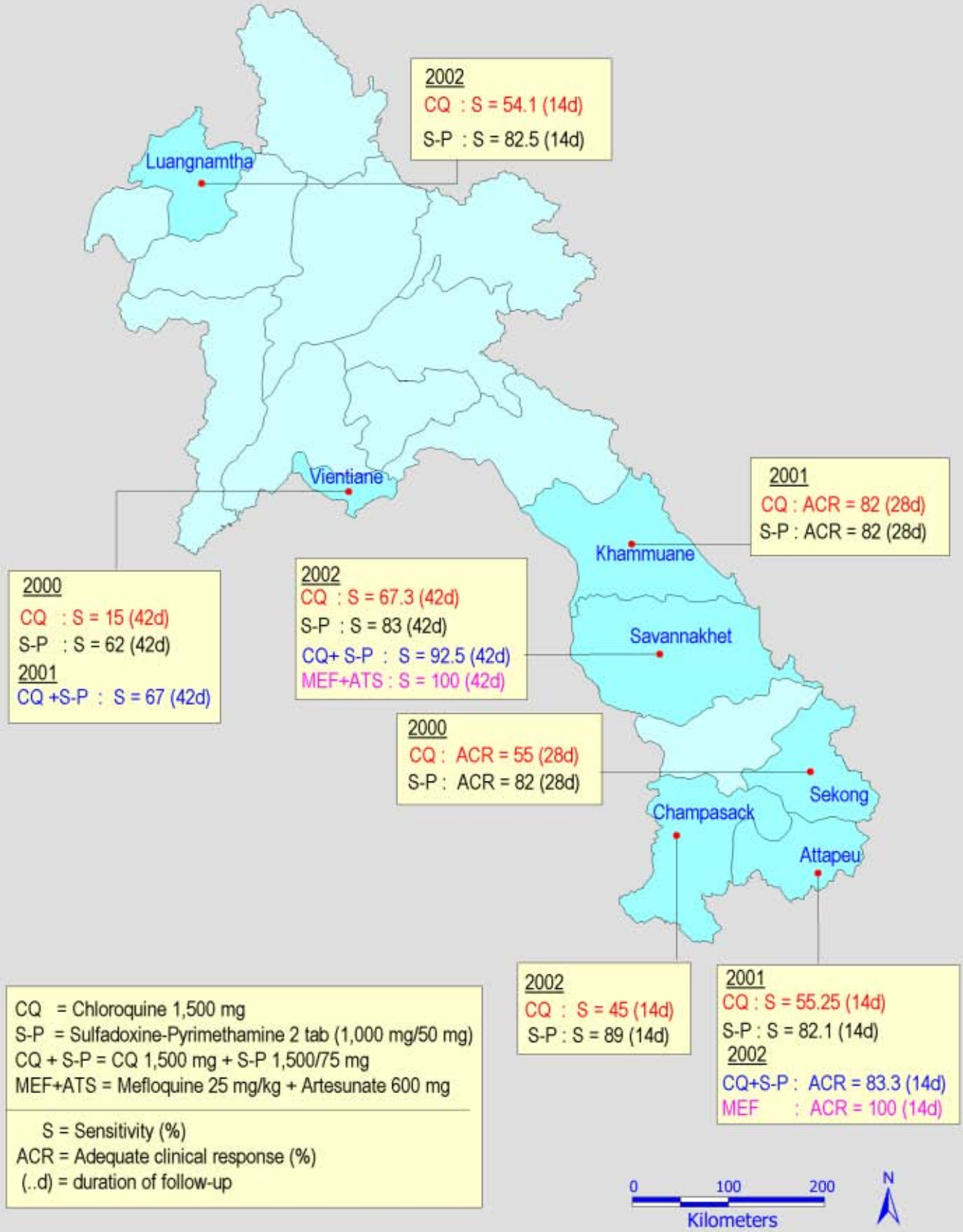

ANTIMALARIAL DRUGS EFFICACY IN LAO PDR
2002
CQ : S = 54.1 (14d)
S-P : S = 82.5 (14d)
Luangnamtha
Vientiane
2001
CQ : ACR = 82 (28d)
S-P : ACR = 82 (28d)
Khammuane
2000
CQ : S = 15 (42d)
S-P : S = 62 (42d)
2001
CQ +S-P : S = 67 (42d)
2002
CQ : S = 67.3 (42d)
S-P : S = 83 (42d)
CQ+ S-P : S = 92.5 (42d)
MEF+ATS : S = 100 (42d)
Savannakhet
2000
CQ : ACR = 55 (28d)
S-P : ACR = 82 (28d)
Sekong
Champasack
Attapeu
2002
CQ : S = 45 (14d)
S-P : S = 89 (14d)
2001
CQ : S = 55.25 (14d)
S-P : S = 82.1 (14d)
2002
CQ+S-P : ACR = 83.3 (14d)
MEF : ACR = 100 (14d)
CQ = Chloroquine 1,500 mg
S-P = Sulfadoxine-Pyrimethamine 2 tab (1,000 mg/50 mg)
CQ + S-P = CQ 1,500 mg + S-P 1,500/75 mg
MEF+ATS = Mefloquine 25 mg/kg + Artesunate 600 mg
S = Sensitivity (%)
ACR = Adequate clinical response (%)
(..d) = duration of follow-up
0
100
200
Kilometers
N

Figure 32

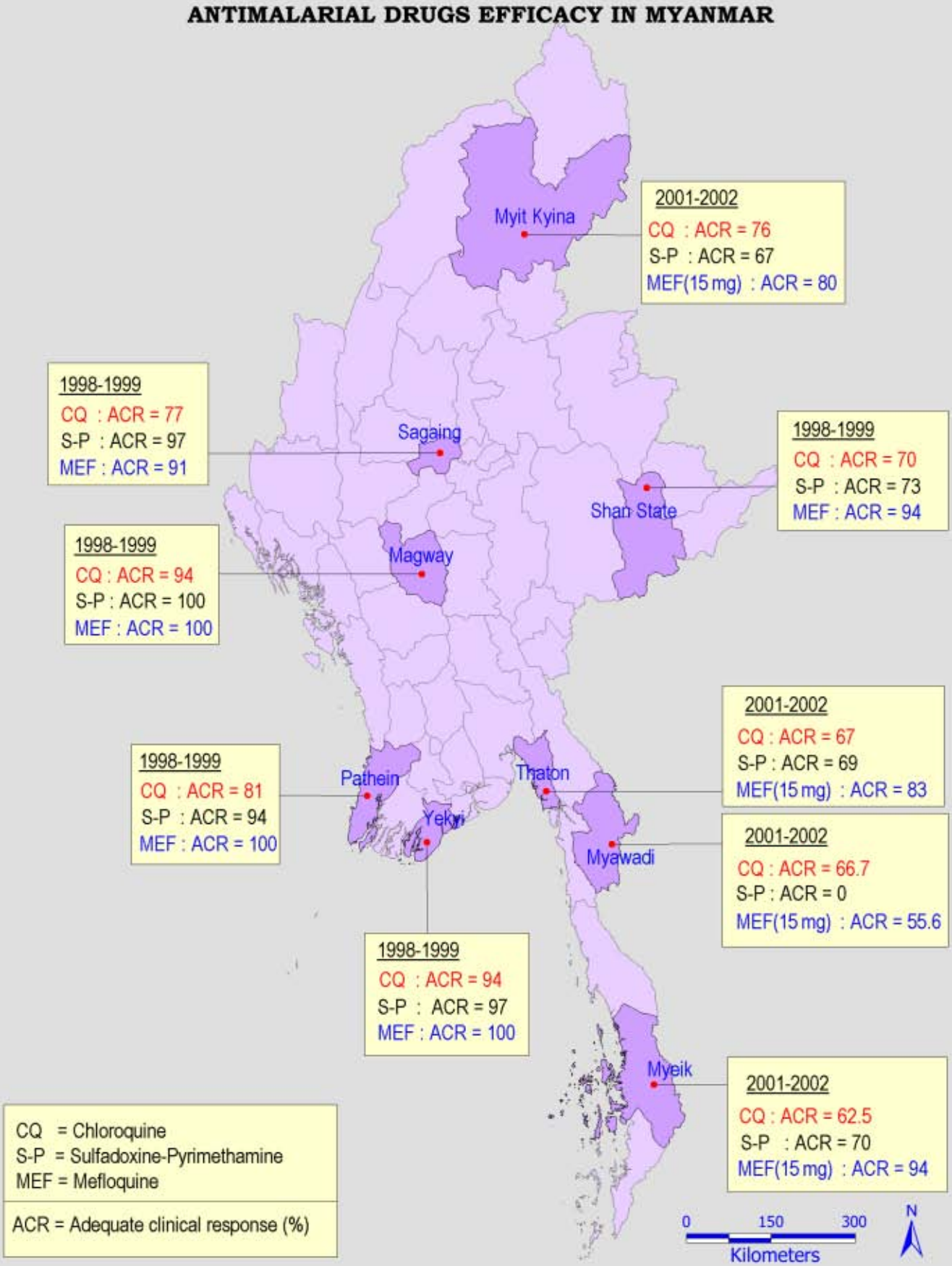

ANTIMALARIAL DRUGS EFFICACY IN MYANMAR
Myit Kyina
2001-2002
CQ : ACR = 76
S-P : ACR = 67
MEF(15 mg) : ACR = 80
1998-1999
CQ : ACR = 77
S-P : ACR = 97
MEF : ACR = 91
Sagaing
1998-1999
CQ : ACR = 70
S-P : ACR = 73
MEF : ACR = 94
Shan State
1998-1999
CQ : ACR = 94
S-P : ACR = 100
MEF : ACR = 100
Magway
2001-2002
CQ : ACR = 67
S-P : ACR = 69
MEF(15 mg) : ACR = 83
1998-1999
CQ : ACR = 81
S-P : ACR = 94
MEF : ACR = 100
Pathein
Thaton
Yekyi
Myawadi
2001-2002
CQ : ACR = 66.7
S-P : ACR = 0
MEF(15 mg) : ACR = 55.6
1998-1999
CQ : ACR = 94
S-P : ACR = 97
MEF : ACR = 100
Myeik
2001-2002
CQ : ACR = 62.5
S-P : ACR = 70
MEF(15 mg) : ACR = 94
CQ = Chloroquine
S-P = Sulfadoxine-Pyrimethamine
MEF = Mefloquine
ACR = Adequate clinical response (%)
0
150
300
Kilometers
N

Figure 33

people due to differing socio-economic conditions. High efficacy was observed (Figure 31b) with other artemesinin-based drug combinations (Artekin, Coartem) in most of the areas where the drugs were tested, with some decline in ACR for Artekin in the year 2002.

Lao PDR (Figure 32): There was moderate efficacy of CQ alone, while S-P alone generally showed a satisfactory response. The combination of CQ + S-P gave a efficacy of 83% - 93% except in Vientiane where it was lower (67%). Mefloquine + artesunate gave 100% efficacy.

Myanmar (Figure 33): In the central part of the country some sites recorded 100% efficacy to mefloquine alone (1998-1999) whereas in eastern sites the response recorded was substantially lower. For instance reduction in efficacy of mefloqunie was observed in Myawadi which is located opposite to Tak Province, which records a similar efficacy (2001-2002). This may be attributed at least in part to the extensive nature of population mobility across the international border in both directions. It is interesting to note that the efficacy to CQ (2001-2002) ranged from 63% to 76%.

Thailand (Figure 34): Mefloquine alone is still effective in some endemic areas but commonly should be used in combination with artesunate or other drugs. The variability in the efficacy to mefloquine alone in Ranong Province, located in the southern part along the Thai-Myanmar border, showed a dramatic decline in therapeutic response from 81% in 2000 to 38% in 2001 and 32% in 2002. This has led to a change in drug policy to a combined therapy with artesunate in 2003. However, mefloquine alone is still recommended to be used along the Thai-Lao and Thai-Malaysian borders.

Viet Nam (Figure 35):The treatment guidelines are different in the north and south of Viet Nam according to the differential distribution of *Pv* and *Pf.* In the northern part the majority of cases are *Pv* while in the central and southern parts *Pf* predominates. Thus, in the north probable malaria (unconfirmed) is treated with chloroquine while probable malaria in the south/central part of the country is treated with artemisinin/artesunate. Confirmed falciparum cases in the north are treated with artemisinin/artesunate for 5 days while confirmed falciparum malaria cases in the south/central part are treated with mefloquine + artesunate for 3 days. As shown in Figure 35, the mefloquine-artesunate combination showed 100% efficacy in all areas tested in the year 2000. More detailed information on drug efficacy/resistance based on therapeutic responsiveness is given in Appendix 2.

So far the advent of the sentinel sites strategy would seem to have had a good start. If and when all the sites are being regularly monitored and reported, it should be possible to envisage a very substantial picture of drug efficacy and resistance evolving for

the region, so eventually to lead to a region-wide drug policy development. However, the resistant drug scenario continues to threaten, necessitating development of revised treatment policy to optimize drug usage. To this effect, the Thai program has established a multi-site policy that stratifies the endemic areas according to mefloquine efficacy/resistance in order to continue the use of mefloquine where it is still effective or mefloquine + artesunate where the single drug is less so. The strategy is depicted in Figure 36.

While drug combinations offer some immediate hope, it would seem to be inappropriate to rely too entirely on existing options in the long run. Hopefully the more systematic reporting of drug efficacy using the sentinel site strategy will lead to a more reliable database for drug efficacy and resistance. The fear is that multi-drug resistance generated in this region will spread rapidly to most endemic countries, the challenge is to use all possible counteracting approaches (Wongsrichanalai *et al*, 2002).

The rapid progress of molecular epidemiology of CQ and S-P mutants has identified markers in parasite isolates that can be traced across the world (Wongsrichanalai *et al*, 2002). This development permits more precise time-frame pathway delineation of mutant spread than has previously been feasible. Level of transmission influences the rate and spread of drug resistance but the latter is most probably multifactorial. Current molecular studies suggest the Asian origin of chloroquine-resistant African *Pf* isolates but at least 4 different groups of chloroquine resistant mutants have so far been identified (Wellems and Plowe, 2001). Pursuance of molecular genetic analysis to a wider spectrum of drugs in geographic context should lead to more precise delineation of drug resistance spread from the Mekong region epicenter and thus provide a measure of the effectiveness of concerted multi-country drug policy.

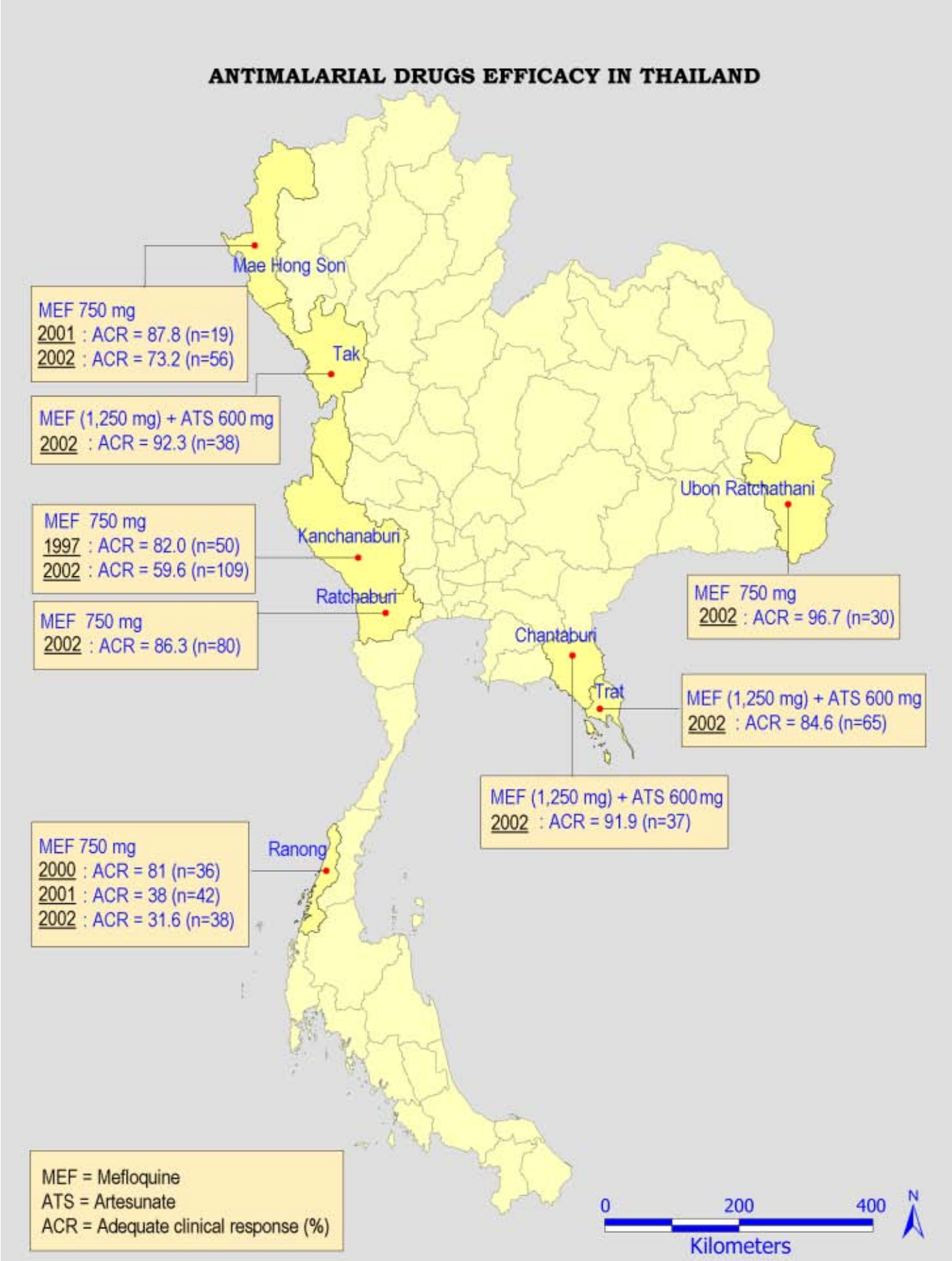

ANTIMALARIAL DRUGS EFFICACY IN THAILAND
Mae Hong Son
MEF 750 mg
2001 : ACR = 87.8 (n=19)
2002 : ACR = 73.2 (n=56)
Tak
MEF (1,250 mg) + ATS 600 mg
2002 : ACR = 92.3 (n=38)
Ubon Ratchathani
MEF 750 mg
1997 : ACR = 82.0 (n=50)
2002 : ACR = 59.6 (n=109)
Kanchanaburi
MEF 750 mg
2002 : ACR = 96.7 (n=30)
Ratchaburi
MEF 750 mg
2002 : ACR = 86.3 (n=80)
Chantaburi
Trat
MEF (1,250 mg) + ATS 600 mg
2002 : ACR = 84.6 (n=65)
MEF (1,250 mg) + ATS 600 mg
2002 : ACR = 91.9 (n=37)
MEF 750 mg
2000 : ACR = 81 (n=36)
2001 : ACR = 38 (n=42)
2002 : ACR = 31.6 (n=38)
Ranong
MEF = Mefloquine
ATS = Artesunate
ACR = Adequate clinical response (%)
0
200
400
Kilometers
N

Figure 34

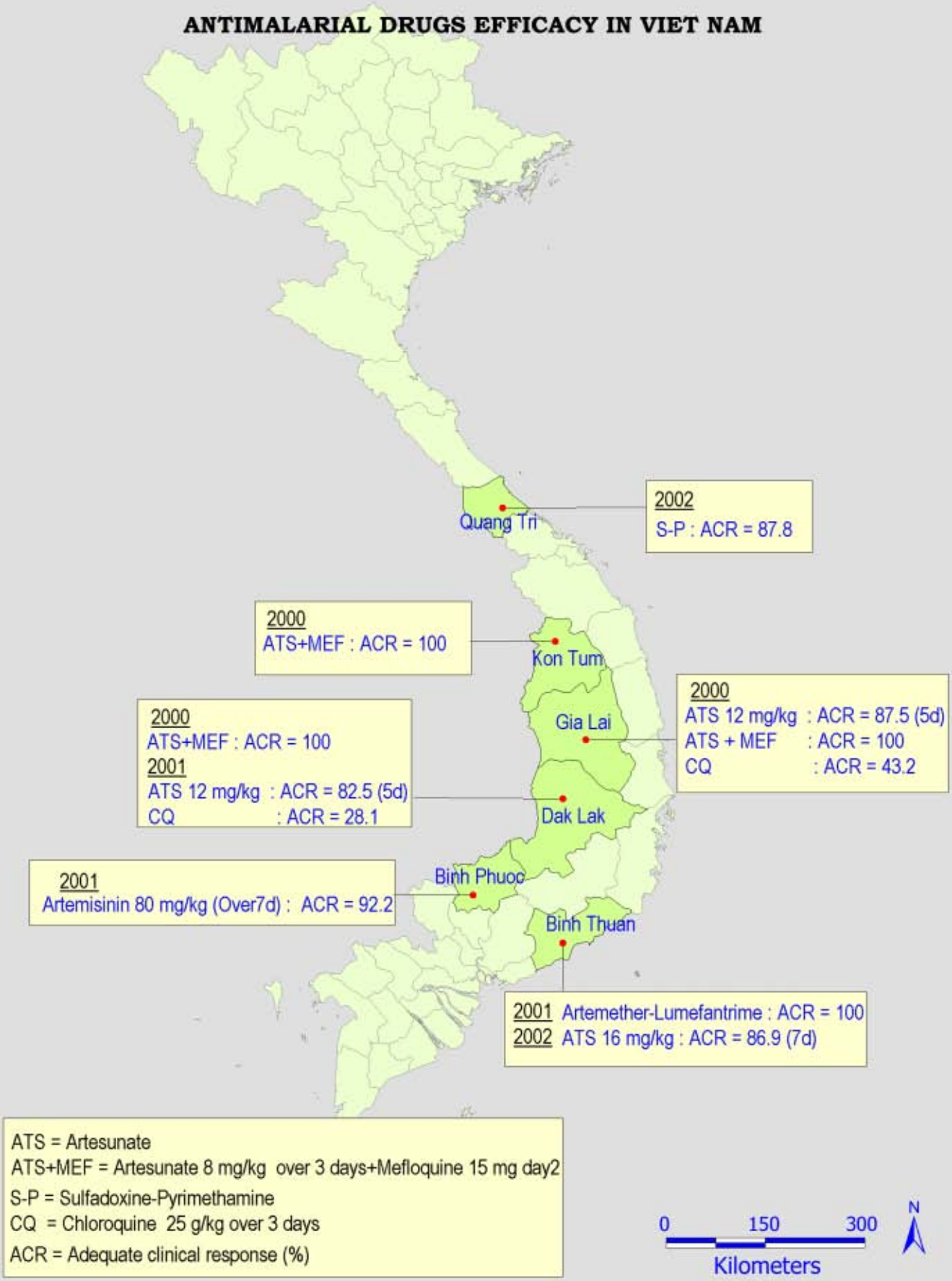

ANTIMALARIAL DRUGS EFFICACY IN VIET NAM
Quang Tri
2002
S-P : ACR = 87.8
2000
ATS+MEF : ACR = 100
Kon Tum
2000
ATS+MEF : ACR = 100
2001
ATS 12 mg/kg : ACR = 82.5 (5d)
CQ : ACR = 28.1
Gia Lai
2000
ATS 12 mg/kg : ACR = 87.5 (5d)
ATS + MEF : ACR = 100
CQ : ACR = 43.2
Dak Lak
2001
Artemisinin 80 mg/kg (Over7d) : ACR = 92.2
Binh Phuoc
Binh Thuan
2001 Artemether-Lumefantrime : ACR = 100
2002 ATS 16 mg/kg : ACR = 86.9 (7d)
ATS = Artesunate
ATS+MEF = Artesunate 8 mg/kg over 3 days+Mefloquine 15 mg day2
S-P = Sulfadoxine-Pyrimethamine
CQ = Chloroquine 25 g/kg over 3 days
ACR = Adequate clinical response (%)
0
150
300
Kilometers
N

Figure 35

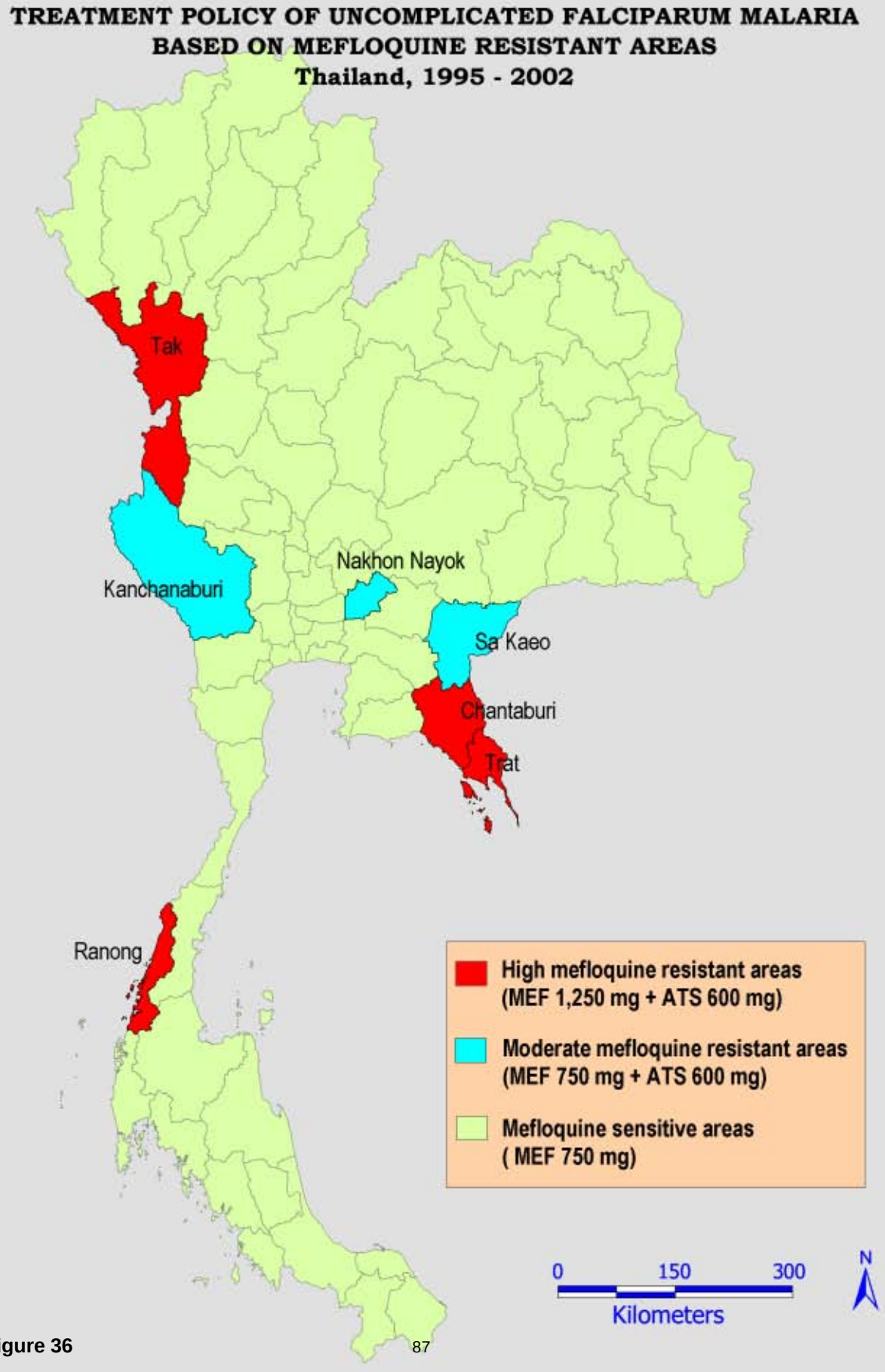

TREATMENT POLICY OF UNCOMPLICATED FALCIPARUM MALARIA
BASED ON MEFLOQUINE RESISTANT AREAS
Thailand, 1995 - 2002
Tak
Kanchanaburi
Nakhon Nayok
Sa Kaeo
Chantaburi
Trat
Ranong
High mefloquine resistant areas
(MEF 1,250 mg + ATS 600 mg)
Moderate mefloquine resistant areas
(MEF 750 mg + ATS 600 mg)
Mefloquine sensitive areas
(MEF 750 mg)
0
150
300
Kilometers
N

Figure 36