

An epidemiological early warning system for malaria control in northern Thailand*

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Parasitological data for the years 1973-81 were examined to determine the years of "acceptable" or "normal" transmission of malaria, for every district of northern Thailand. The monthly mean number of cases and the mean plus 2 standard deviations (SD) were calculated for the selected years and plotted on log-linear graph paper. The resulting graphs were distributed to the Malaria Sector Offices. Sector Chiefs were then responsible for plotting the monthly observed number of cases of malaria as the data became available; if the observed incidence was more than 2 SD greater than the "normal" mean for that month, the Zone and Regional Malaria Offices were informed. Retrospective analysis of data from districts where malaria outbreaks had occurred indicated that the method provides an effective warning of impending epidemics. It is expected that the resulting earlier implementation of appropriate remedial control measures will lead to a reduction in malaria incidence in the region.

Antimalaria operations in northern Thailand started in 1930, when the first malaria unit was opened in Chiangmai to carry out limited malaria surveys and to administer quinine. In 1949 the Government, with WHO/UNICEF assistance, initiated a malaria control pilot project in the plains of Chiangmai province, based on house spraying with DDT. After encouraging results, these activities were expanded in 1951 into a countrywide control programme, with assistance from the US Government. Since 1975, malaria control has been the object of the programme in areas of medium and high receptivity, with eradication as the goal in areas of low receptivity and in those parts of the country already partially integrated with the general medical services.

The Thai antimalaria programme has been beset by many technical, administrative, and financial difficulties. The technical problems include:

(a) resistance of *Plasmodium falciparum* to 4-aminoquinolines, which was first seen in 1960 and is now found in over 90% of isolates throughout the country;^a

(b) resistance of *P. falciparum* to sulfadoxine-pyrimethamine, which is spreading very rapidly as a result of domestic migration and is now seen in approximately 80% of infections (1);

(c) the exophilic behaviour of the principal vectors, *Anopheles dirus*^b and *A. minimus* (2). Preliminary data indicate that *A. minimus* in the forested foothills of northern Thailand is strongly deterred from resting on DDT-sprayed surfaces, but that DDT does, nevertheless, afford considerable protection by diverting the mosquitos to bite cattle rather than man (S. Nutsathapana, unpublished observations, 1982);

(d) uncontrolled forest clearance for agriculture (and illicit mining and logging operations); the population in these areas live in temporary, usually unsprayed, shelters and are thus exposed to *A. dirus* without adequate protection.

Despite these difficulties, malaria control activities in northern Thailand have generally been remarkably successful.^c During the period 1975-80 the annual parasite incidence (API) varied between 4.5 and 6.0 per thousand, and except during limited outbreaks, was always at or below the lower end of this range. When outbreaks have occurred, the delay in recognizing the accelerating incidence has resulted in failure to implement the necessary remedial measures in time. Thus, quite severe outbreaks, ranging from a very few to hundreds of cases per year, have occurred in fairly

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^a Report of Second Review Meeting of Research Workers in the Regional Collaborative Studies, Kuala Lumpur, Malaysia, 10-15 August 1981. Geneva, World Health Organization, 1981 (Unpublished document, SEA/MAL/138).

^b Formerly called *Anopheles balabacensis*.

^c Report of an independent assessment team. Thailand, Ministry of Public Health, Malaria Division, 1979 (Unpublished document).

Table 1. Annual number of malaria cases in two districts of northern Thailand, 1973-81

District	No. of cases ^a per annum								
	1973	1974	1975	1976	1977	1978	1979	1980	1981
Li	402	353	472	428	1115	1030	386	221	549
Mae Ai	55	43	32	29	59	46	201	921	164

^a Slide-positive for *P. falciparum* or *P. vivax*.

small areas. This is clearly shown in Table 1, which summarizes the incidence of malaria in two districts of the northern region.

Even though the monthly number of cases in a district may be available at sector level within 3-4 weeks of the end of each month, the reasons for the delay in recognizing an outbreak are easy to understand. They include:

(a) the absence of a yardstick against which the current month's data can be measured;

(b) the lack of epidemiological expertise at sector and zone levels;

(c) long delays in reporting from sector through zone, to regional level, where decisions concerning action are taken;

(d) an overburdened regional epidemiology section. As a result there is considerable delay in comparing yearly malaria incidence, district by district.

It is apparent that there is an urgent need for an early warning system to overcome these difficulties, and to permit the more rational application of control measures. Ideally, such a system should be simple enough to be applied at the lowest level of the malaria control organization (i.e., at sector level), reliable enough to indicate abnormal numbers of cases in limited areas, and sensitive enough to give timely warning of impending outbreaks.

An epidemiological monitoring system which appears to meet these criteria has been developed for use in northern Thailand.

METHODS

The antimalaria programme in Thailand is a Division of the Department of Communicable Diseases Control of the Ministry of Public Health. The programme covers five regions, each under the control of a Regional Director. Operationally, region 2 of the Malaria Division (northern Thailand) is divided into zones and sectors, while the area is administratively divided into provinces and districts. The numbers of these divisions, together with the relevant population figures, are summarized in Table 2.

Table 2. Malaria division and government administrative organization of northern Thailand

	Malaria division			Government administration		
	Organizational unit	No.	Average population	Organizational unit	No.	Average population
Zone	6	1 208 600		Province	13	557 820
Sector	62	116 960		District	120	60 430

The population of a sector was considered too numerous and disperse for use as the basic epidemiological unit. Outbreaks in these areas of unstable malaria transmission, which have been under malaria eradication or control operations for 20 years or more, often occur in very limited foci, sometimes in a cluster of only a few villages. When this happens the significance of the outbreak is frequently overlooked, particularly when the data are grouped with figures for the entire sector. Fortunately, the record-keeping in region 2 has been excellent and the number of malaria cases by district, and by month, is available for most districts as far back as 1973. Furthermore, the sectors are normally comprised of a discrete number of districts, common boundaries being used, and this permits analysis of district data at sector level. Since there are, on average, only two districts per sector, this is not an onerous task. Administrative districts are further divided into cantons (average population, 7550), but with the degree of endemicity in northern Thailand it is not necessary to attempt evaluation at cantonal level. However, this would be necessary in areas of higher endemicity, where outbreaks in one canton might be masked by normal, or lower than normal, transmission in other cantons of the same district.

The monthly data for the districts of Li and Mae Ai in northern Thailand for 1973-81 are presented in Tables 3 and 4. The figures show that malaria was reasonably well controlled in Li district during 1973-76 and that an outbreak occurred in 1977-78. In Mae Ai district, control was excellent during the

Table 3. Number of malaria cases per month for the years 1973–81 in Li district of northern Thailand

Year	Jan.	Feb.	Mar.	Apr.	May	June	July	Aug.	Sep.	Oct.	Nov.	Dec.	Total
1973	10	11	7	12	17	51	90	77	41	30	41	15	402
1974	8	3	2	3	31	37	62	47	38	19	38	65	353
1975	21	15	7	12	13	33	91	102	73	43	27	35	472
1976	24	7	2	7	11	16	55	38	65	55	86	62	428
1977	48	15	9	24	35	132	116	167	192	173	83	121	1115
1978	82	28	41	11	44	39	131	122	204	150	134	44	1030
1979	46	40	29	20	10	29	47	46	42	28	23	26	386
1980	9	15	8	18	5	10	22	30	41	47	2	14	221
1981	1	6	11	8	8	26	68	56	104	110	109	42	549
Sum ^a	63	36	18	34	72	137	298	264	217	147	192	177	1655
Mean ^a	15.8	9.0	4.5	8.5	18.0	34.3	74.5	66.0	54.3	36.8	48.0	44.3	34.5
Standard deviation (SD) ^a	7.9	5.2	2.9	4.4	9.0	14.4	18.7	29.2	17.4	15.6	26.0	23.7	27.2
Mean + 2 SD ^a	32	19.3	10.3	17.2	36	63	112	124	89	68	100	92	89

^a Calculated for the years 1973–76.

Table 4. Number of malaria cases per month for the years 1973–81 in Mae Ai district of northern Thailand

Year	Jan.	Feb.	Mar.	Apr.	May	June	July	Aug.	Sep.	Oct.	Nov.	Dec.	Total
1973	1	1	4	6	0	7	7	2	9	7	4	7	55
1974	11	1	1	0	2	2	3	4	6	1	10	2	43
1975	4	1	0	0	1	3	7	1	0	4	5	6	32
1976	1	5	4	0	0	3	2	0	4	4	0	6	29
1977	3	3	0	3	6	10	2	2	10	8	2	10	59
1978	4	1	0	6	1	2	2	3	3	4	10	10	46
1979	4	14	11	4	3	19	55	35	11	5	14	26	201
1980	20	7	2	9	29	244	437	40	23	41	28	41	921
1981	45	21	19	0	10	9	12	14	5	3	13	13	164
Sum ^a	24	12	9	15	10	27	23	12	32	28	31	41	264
Mean ^a	4.0	2.0	1.5	2.5	1.7	4.5	3.8	2.0	5.3	4.7	5.2	6.8	3.7
Standard deviation (SD) ^a	3.7	1.7	2.0	2.9	2.3	3.3	2.5	1.4	3.8	2.5	4.1	3.0	3.1
Mean + 2 SD ^a	11.4	5.3	5.5	8.4	6.2	11.0	8.8	4.8	12.9	9.7	13.4	12.8	9.9

^a Calculated for the years 1973–78.

period 1973–78 with an outbreak beginning in 1979 and recurring at a higher level in 1980.

Thus, statistics for the “base years” (1973–76 for Li district and 1973–78 for Mae Ai district) were con-

sidered to indicate levels of malaria acceptable by control standards. It was necessary, therefore, using the data from these years, to develop a system of analysis that would provide a timely indication of any signifi-

cant increase in the monthly incidence of malaria cases and, hence, a warning of the possible onset of an outbreak.

Several methods of data analysis were assessed using the mean number of cases and standard deviation (SD) for the base years. It can be expected that 95% of "normal" monthly totals of cases will fall within ± 2 SD of the mean. In effect, this implies that 97.5% of monthly "normal" figures will fall below the mean plus 2 SD. Furthermore, only 1% of monthly levels would be expected to surpass the mean + 2.3 SD limit and only 0.1% to go above the mean + 3.1 SD.

The methods of analysis considered are listed below.

Overall mean

The mean number of cases per month was calculated using data for all the months of the base years (i.e., Li district, $n = 48$; Mae Ai district, $n = 72$), and the mean and mean + 2 SD were plotted (Fig. 1c). While this method has the advantage of extreme simplicity, the SD is unacceptably high. Highly significant increases (e.g., that occurring in Li District in January 1977) may, in fact, fall within the limits of this straight line graph.

Moving mean

The data were analysed using a 3-month moving mean in an attempt to obtain a smooth curve, while reflecting seasonality (Fig. 1d). The SD was again too high and when this is combined with the errors likely to arise from calculation of the moving means at sector level, the method was not considered promising.

Cumulative mean

Monthly means were added consecutively, and the respective SDs calculated (Fig. 1e). Although this method takes some account of seasonality, it is subject to considerable distortion by unusually large, or small, observed numbers of cases occurring early in the year. It was, therefore, likewise discarded.

Monthly mean

The method chosen for use in northern Thailand takes account of monthly variations in "normal" transmission. The monthly means and standard deviations for the base years were calculated for each district. A graph was drawn (see Fig. 1a and b) showing the monthly variation in mean and mean + 2 SD. This graph is the annual "normal" distribution for the district. The annual graph is repeated across the graph paper for as many years as can be accommodated.

A normal graph was prepared by the Regional Epidemiology Section for the period January 1981–April

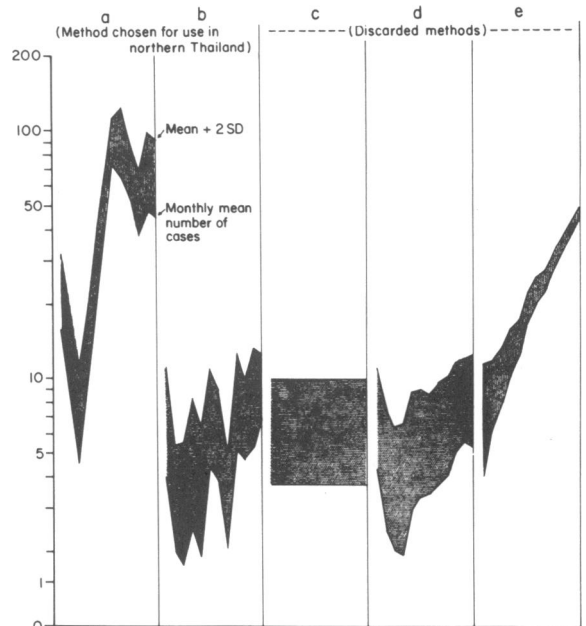


Fig. 1. Methods of analysis evaluated for use in the early warning system for malaria in northern Thailand: a — monthly mean and mean + 2 SD (Li district); b — monthly mean and mean + 2 SD (Mae Ai district); c — overall mean and mean + 2 SD (Mae Ai); d — moving mean and mean + 2 SD (Mae Ai); e — cumulative mean and mean + 2 SD (Mae Ai).

1987, for each district for which 4 or more base years of data were available. When only 3 base years of data were available, the normal graph was prepared for January 1981–December 1983 only, at which time the data were re-examined and, if necessary, re-analysed to prepare new normal graphs. Finally, the staff of the Epidemiology Section plotted the observed monthly numbers of cases for 1981, as a guide for the Sector Chief.

The prepared graph was then sent to the Sector Chief, who was thereafter responsible for continuing to plot the actual monthly numbers of cases, as soon as they became available. He was instructed to inform both the Zone Chief and the Regional Director and/or Epidemiologist immediately if the number of cases exceeded the normal mean + 2 SD for that month.

In the event of such a "breakthrough", an evaluation is made by the regional authorities, together with the Zone Chief. As a first step, they examine three aspects of the occurrence, namely;

- the number of SD by which the incidence exceeds the predicted mean for that month;
- the frequency of breakthrough, i.e., the number of times the level has surpassed the mean + 2 SD in the previous 2 years; and

(c) the trend of the plot of number of cases in the months immediately preceding the breakthrough.

If it is concluded that an outbreak is beginning, then further evaluation is necessary. This involves a thorough analysis of the situation, an examination of the control measures to be applied (for both the short-term control of the current epidemic and the long-term prevention of a recurrence), and subsequent evaluation of the measures applied.^d

If, on the other hand, it is believed that there is insufficient evidence to indicate an outbreak, the Sector Chief is instructed to maintain extra vigilance and report any figures that approach the upper limit, as well as those that exceed it. A continuous upward trend or another breakthrough within a few months would indicate the beginning of an outbreak.

Data analysis

Fig. 2 shows the Li district normal graph calculated from the base years 1973–76 and the actual monthly number of cases for 1973–81; Fig. 3 shows the equivalent plots for Mae Ai district (base years 1973–78 and actual figures for 1973–81).

^d MOLINEAUX, L. *Modules for action in major causes of epidemics: malaria*. Geneva, World Health Organization, 1981 (Unpublished document, CDS/Mtg./Mod./81.9).

When the data for Li district are examined, it can be seen that the number of cases in January 1977 was significantly higher than expected. A more detailed study of this month's data (Table 3) reveals that the expected mean was 15.8 (SD, 7.9) and the actual number of cases, 48. This is 4 SD beyond the mean and must, therefore, be considered highly significant.

Further examination of the graph for Li district shows a reasonably good fit during 1973–75, but there are signs of an upward trend in the number of cases during the last few months of 1976. This, together with the 48 cases in January 1977, would normally be sufficient to precipitate immediate remedial action. Even if the trend were ignored and the return to normal limits in February and March noted, the high level in April (3.5 SD above the mean) should be sufficient to remove any lingering doubts that an outbreak was actually beginning.

Had the significance of the situation been realized in May–June 1977, when the January and April figures were available at the sector level, remedial measures could have been introduced at once, instead of in February 1979, as was actually the case.

The indications of a breakdown in control in Mae Ai (Fig. 3) are even more pronounced. The "normal" curve is calculated from six base years instead of only four and, therefore, has more validity than that for Li

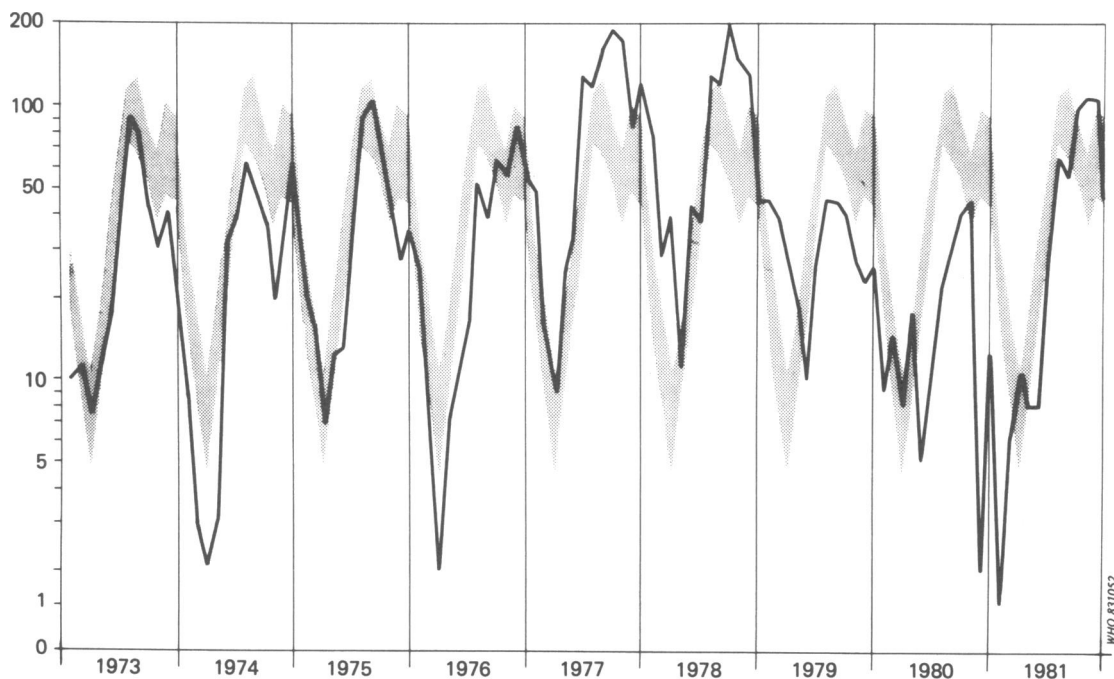


Fig. 2. "Normal" graph, based on 1973–76, and observed number of cases for 1973–81, for Li district.

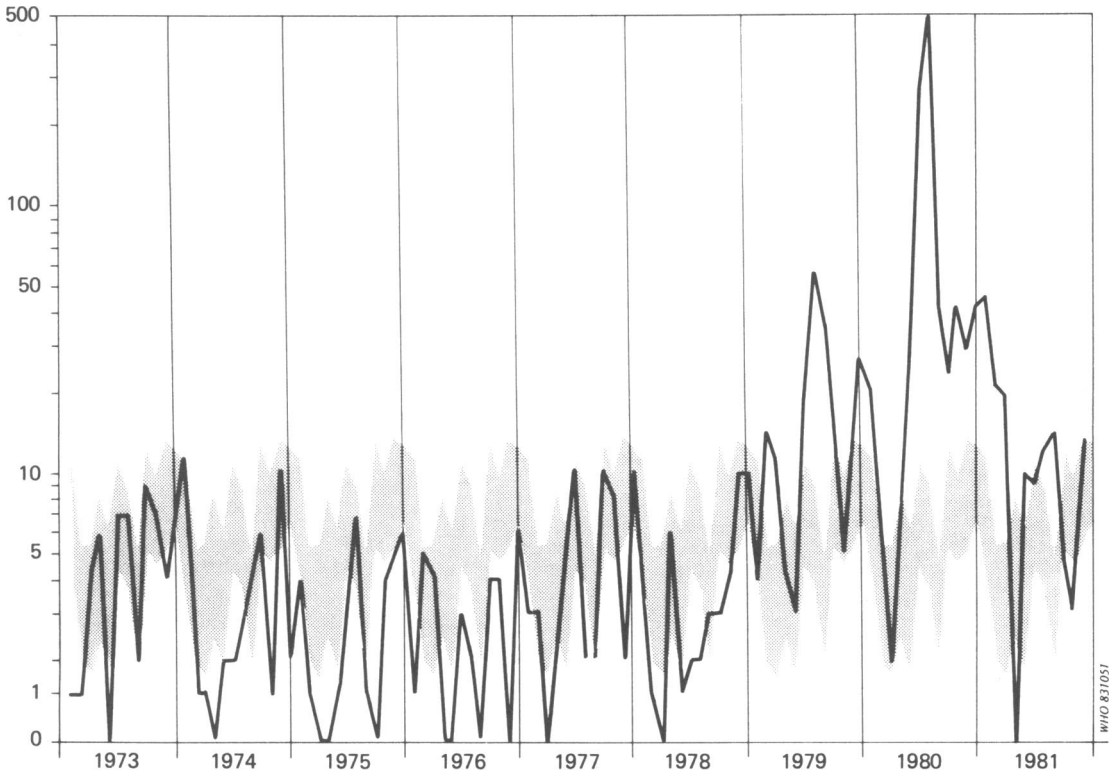


Fig. 3. "Normal" graph, based on 1973-78, and observed number of cases for 1973-81, for Mae Ai district.

district. Once again there was an apparent upward trend towards the end of 1978. In February 1979 there were 14 cases (7 SD above the mean) and in March, 11 cases (4.75 SD), ample evidence that an outbreak was beginning, even considering the drop that occurred in April and May.

In view of the small sample sizes used in computing the normal graphs, it is appropriate to use Student's t distribution to determine the significance of breakthroughs. In Li district (number of base-years, 4) the numbers of cases for January and April 1977 are found to lie between $t_{0.975}$ and $t_{0.99}$. Thus, both the levels of significance and their juxtaposition must still be considered to be very strong indications for intervention. As would be expected, the breakthroughs in Mae Ai district were more highly significant. Both the February and March 1979 figures exceeded the $t_{0.995}$ level, thus confirming the beginning of an outbreak.

Despite the small sample sizes it has been thought advisable to maintain the mean + 2 SD for the upper limit, even though some breakthroughs at this level are false alarms. An analysis of data from 114 districts, showing the number and level of break-

throughs not associated with epidemics, is given in Table 5.

It can be noted that, while the total number of observed breakthroughs is very close to the expected

Table 5. Analysis of breakthroughs, not associated with epidemics, in 114 districts during 1973-81

Mean annual no. of cases in the district	No. of "control" months	No. of observed breakthroughs ^a			Total
		2.0-2.3 SD	2.3-3.1 SD	> 3.1 SD	
< 50	3232	57 (49)	62 (29)	7 (3)	126 (81)
51-100	1744	33 (27)	23 (15)	5 (2)	61 (44)
> 100	4140	26 (63)	14 (37)	10 (4)	50 (104)
Total	9116	116 (137)	99 (82)	22 (9)	237 (228)

^a Figure in parentheses gives expected number of breakthroughs.

number (237 and 228, respectively), there is considerable variation depending on the mean annual number of cases in the district and also on the level of the breakthrough.

In the districts with a low or medium incidence of malaria, i.e., with fewer than 50 or between 51 and 100 cases per year, the numbers of breakthroughs greatly exceed the expected: 126 (expected, 81) and 61 (expected, 44), respectively. This result is not surprising; when the monthly mean number of cases is low, and the variance is correspondingly small, an increase of even one case can assume a spurious statistical significance. The epidemiologist should have no difficulty in determining the importance of the observations and deciding what action to take. When the incidence is high (over 100 cases per year), the observed number of breakthroughs was less than expected, except at the > 3.1 SD level, and this can be explained by the large variance resulting from wide fluctuations in the monthly number of cases.

The question of the excess number of breakthroughs at the 3.1 SD level is perhaps more serious and may present the epidemiologist with some problems. However, of the 22 breakthroughs at this level, 7 occurred late in 1981 and might have been the first indications of epidemics, 4 were associated with an abnormally high number of slide collections, and 2 were associated with very low transmission rates. It would seem, therefore, that a careful study of all the data, including the plot for the preceding months and the juxtaposition of other breakthroughs, both before and after the observation concerned, would help to resolve any difficulties of interpretation.

DISCUSSION AND CONCLUSIONS

The warning system described above is an adaptation to malaria of an old principle used in the definition of epidemic indices (3). The monthly mean method, used here retrospectively, gives excellent indications of the beginnings of outbreaks. In the 114 districts for which data are available, 95 outbreaks occurred for which the system would have given early warnings. These outbreaks involved some 71 000 "excess" cases (i.e., above the normal annual mean), or 23% of the total number of cases during the period 1973-81. If application of the early warning system resulted in a reduction of only half these excess cases, this would mean an overall decrease of more than 11% in malaria incidence.

The system, which has been operational in all districts of northern Thailand since June 1982, also focuses attention on the districts that require

improved control activities, where the level of endemicity is already unacceptably high. Whenever improved control is achieved, a revision of the baseline data will be required. Thus, it is hoped that application of the system will lead to a more rational allocation of preventive measures, within budget limitations, and an eventual overall reduction in malaria.

Direct evaluation of the impact of the early warning system may prove difficult. Exact comparison with the previous situation is virtually impossible, because of the different etiology of every outbreak. This would be particularly true, for example, when the appearance of drug-resistant strains of plasmodia is wholly, or partly, responsible for an increase in transmission. An outbreak due entirely to resistant strains would presumably be of lesser dimensions than one where the appearance of resistance coincided with a real increase in vectorial capacity.

However, prompt evaluation of every indicated breakthrough and the immediate application of appropriate control measures in all districts must lead to improved control and a corresponding reduction in malaria incidence.

Changes in the methods or performance of case detection will undoubtedly introduce biases into the warning system. It is important, therefore, to be aware of such changes and to take them into account when setting up, using, or revising the system.

The incorporation of other parameters, such as those described by Onori & Grab (4) using direct (man-biting rates, daily survival rates, etc.) and indirect (mostly meteorological) observations could increase the usefulness of the system. While addition of the indirect factors is easy, inclusion of the entomological parameters may require a sophistication of techniques and interpretation that is not always available.

The early warning system shows considerable promise for northern Thailand and most of the remainder of the country, within the limitations already discussed. Its application in other countries will depend on the level and quality of the surveillance, the degree of transmission, the number of years of retrospective data available for analysis and, possibly, the principal vectors responsible for transmission.

Finally, it should be repeated that the early warning system described is only the first step in preventing epidemics. Once careful analysis of the data has been made and it has been decided that an outbreak is beginning, a full epidemiological investigation is necessary to establish the location and extent of the outbreak, the species involved, the likely causes, and the appropriate control measures.

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RÉSUMÉ

UN SYSTÈME ÉPIDÉMIOLOGIQUE DE PRÉ-ALERTE POUR
LA LUTTE ANTIPALUDIQUE DANS LE NORD DE LA THAÏLANDE

On a constaté en Thaïlande que les flambées de paludisme sévissaient bien avant que les responsables de la surveillance et de la planification en poste dans les Bureaux régionaux du Paludisme en prennent connaissance. Dans certains cas, c'est avec un retard de deux ans qu'elles étaient dépistées. Afin de réduire ce délai, un «système de pré-alerte» a été mis au point pour déceler les tendances dans la transmission du paludisme. Ce système consiste à comptabiliser chaque mois les cas de paludisme et à déterminer les écarts types correspondants (50) pendant les années de transmission «normale». Les chiffres mensuels concernant le paludisme

sont totalisés par le personnel de chaque secteur, puis comparés à l'aide d'un graphique avec les chiffres prévus pour le mois considéré. Si les chiffres réels sont constamment supérieurs de plus de deux écarts types à la moyenne pour ce mois, les services de surveillance sont avisés et, si besoin est, des mesures de lutte spécifiques sont préparées.

Ce système est désormais opérationnel dans tous les districts de la Région Nord de la Thaïlande et dans de nombreuses autres parties du pays. On espère ainsi obtenir un dépistage plus précoce des poussées épidémiques et, de ce fait une réduction de l'incidence du paludisme.

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