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Treatment Failure in Filariasis Mass Treatment Programmes *

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The data from the first 3 years of the Samoan pilot filariasis control programme were reanalysed using incidence instead of prevalence statistics. With these statistics, failures of diethylcarbamazine treatment can be roughly divided into three groups: primary treatment failures, manifested by persistent microfilaraemia; secondary treatment failures, manifested by microfilaraemia recurring within the prepatent period after apparently successful treatment; and new infections. When cases of persistent and recurrent microfilaraemia are excluded by appropriate statistical manipulations, the incidence of new infections is seen to be many times higher in persons who originally showed microfilaraemia. This suggests that susceptibility or exposure, or both, are not homogeneously distributed in the population, and indicates that proposed mathematical models of filarial epidemiology must be further refined. It also indicates that filariasis control programmes should devote more attention to studies and control methods aimed at this high-risk subgroup of the population.

The advent of mass treatment programmes using diethylcarbamazine (DEC) for filariasis control has given rise to several new questions in the epidemiology of the disease. Though DEC is a safe and effective agent for lowering microfilaria rates, it does not always produce complete clearing of microfilaraemia (MF) in all treated individuals (Hawking, 1962). We are aware of only one published report (Fukushima, 1967) of complete eradication of filarial infection in a population by DEC treatment alone. Such difficulties point to unsolved problems that require special attention in filariasis control or eradication programmes.

Filariasis is usually diagnosed in individuals by means of a thick blood film of 20–60 mm³. If microfilariae are found (i.e., the individual is " positive ") it is clear that the person has filariasis. If no microfilariae are found it is not certain that the individual is not infected. Commonly, he may be " negative " because the density of microfilariae is at that moment below the threshold of detection. Alternatively, he might truly be blood negative but infected with unmated parasites; this, however, is probably not of much clinical significance. Both of these types of false negative decrease the sensitivity of the test.

Filariasis is generally measured in populations by means of the microfilaria rate. This statistic is simply the point prevalence of microfilaraemia, or the proportion " positive " in the population. Because of the insensitivity of the test, prevalence figures represent underestimates of true prevalence, especially when microfilaria densities are low, as after mass treatment with DEC. Incidence rates measure the proportion of known negatives converting to positive within a given period of time. Reversion rates measure the proportion of known positives reverting to negative during a given period of time. Neither incidence nor reversion rates are widely used in filariasis epidemiology; at the usual levels of prevalence and sensitivity both measurements represent slight overestimates of incidence and of reversion.

There are important objections to the exclusive use of prevalence data. Current prevalence is a valid index of risk of infection only under conditions of equilibrium, when both incidence and reversion remain constant. If control or eradication programmes

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are to disturb this equilibrium, especially by treating microfilaraemia, it is essential to monitor current incidence as well as prevalence. Hairston & Jachowski (1968) have estimated the incidence of microfilaraemia under equilibrium conditions by use of the catalytic models of Muench (1959). Because of unpredictable changes in rates of incidence and reversion, these models are not directly applicable to treatment programmes. Incidence can be measured directly, however, and is a more useful statistic to describe and analyse the results of DEC treatment.

Previous authors have suggested different mechanisms by which microfilaraemia following DEC treatment could be related either to inefficacy of the treatment on certain forms of the parasite or to subsequently acquired infection (Otto, Jachowski & Wharton, 1953; McGregor & Gilles, 1956). Incidence data from the pilot control programme in American Samoa suggest that not one but several processes are responsible for these apparent treatment failures. Other authors have used the terms " persistent microfilaraemia ", " recurrence ", " new infection ", and " reinfection " to describe overlapping concepts of treatment failure. We have redefined these terms, generally in a narrower sense than the original authors intended, in order to describe these processes separately.

Table 1. Persistent microfilaraemia among original positives in four Samoan villages one week after diethylcarbamazine treatment

Risk factor	No. treated	No. positive at 1 week	Persistence (%)
Pretreatment MF/20 mm³ [a]			
1–10	61	1	2
11–50	53	22	41
51–100	23	9	39
101–200	25	16	64
⩾201	13	8	62
all levels	175	56	32
Age group [b]			
0–9	23	8	35
10–19	47	16	34
20–29	27	10	37
30–39	22	5	23
⩾40	56	17	30
all ages	175	56	32
Sex [c]			
male	93	29	31
female	82	27	33
both sexes	175	56	32

[a] Highly significant: $\chi^2 = 45.6$, 4 df, $P < 0.001$.
[b] Not significant: $\chi^2 = 1.4$, 4 df, $P > 0.8$.
[c] Not significant: $Z = 0.25$, $P = 0.8$.

PERSISTENT MICROFILARAEMIA

A number of individuals originally positive show microfilaraemia during or immediately after commonly used courses of treatment with DEC. These we call persistent MF. These cases must be identified before seeking other causes of apparent treatment failure. Table 1 analyses the occurrence of persistent MF within one week of treatment in four Samoan villages. At this dosage level (6 mg/kg for 6 days), the proportion of persistent MF rises significantly with pretreatment microfilarial density. Age and sex seem to have no important effect. These persistent microfilaraemias suggest that the treatment did not kill all circulating microfilariae, but do not provide information about any effect on adult parasites. Prevalence data are adequate to describe persistent MF, but incidence data are necessary to distinguish it from other phenomena.

RECURRENCE

We will use this term to describe the reappearance, after apparently successful treatment, of microfilariae arising from previous infections.

The clearance of microfilaraemia shows that DEC is effective on circulating microfilariae. The return of microfilaraemia within an interval shorter than the prepatent period (generally agreed to be somewhat less than a year) may be explained by a number of hypotheses: (1) that adult parasites were not affected at all by treatment; (2) that adult parasites were reversibly damaged or sterilized by treatment, but have regained some reproductive capacity; or (3) that juvenile parasites present during treatment were not affected by treatment and have since begun reproduction (Otto, Jachowski & Wharton, 1953; McGregor & Gilles, 1956). In any of these cases, recurrence within the prepatent period implies that the drug is effective on microfilariae but is not completely effective on adult or juvenile forms.

Table 2. Recurrences within one year of treatment among treated positives in four Samoan villages. Individuals positive one week after treatment are excluded

Risk factor	No. at risk [a]	No. of incident cases [b]	Recurrence rate (%)
Pretreatment MF/20 mm³ [c]			
1–10	55	5	9
11–50	30	10	33
⩾51	26	12	46
all levels	111	27	24
Village [d]			
Amanave	31	10	32
Amouli	22	9	41
Aoa	16	5	31
Malaeloa	42	3	7
all villages	111	27	24
Time of recurrence [e]			
first 6 months	111	23	21
second 6 months	88[f]	4	5
entire year	111	27	24

[a] Negative at week 1.
[b] Positive at 6 months or at 1 year.
[c] Highly significant: $\chi^2 = 15.0$, 2 df, $P<0.001$.
[d] Significant: $\chi^2 = 11.5$, 3 df, $P<0.01$.
[e] Highly significant: $Z = 3.57$, $P<0.001$.
[f] Negative at week 1 and at 6-month survey.

The phenomenon of recurrence is real, but cannot be revealed by the usual prevalence data because the time of reconversion to positive is not known. One can follow groups of treated positives, however, and monitor the incidence of MF during particular periods of time, among persons negative at the beginning of each period. By this strategy one can exclude from consideration " persistents " who never revert to negative upon treatment, and identify " recurrences " who do revert to negative at the time of treatment, but again become positive within the prepatent period. These recurrences should become manifest in a time shorter than the prepatent period, because the full time for parasites to grow from infective larvae to maturity is not required (Hairston, personal communication); the incidence of recurrence might also reach a peak at some time within the prepatent period, and then decline as the subpopulation of inadequately treated positives is depleted by discovered recurrences. Examination of incidence rates within the year following treatment can show whether these things occur.

In four villages involved in the Samoan pilot programme, 119 of 175 original positives became negative 1 week after receiving 5–6 doses of 6 mg of DEC per kg of body weight. Subsequent recurrence during the first year was assessed with a sample of 111 treated positives who became negative just after treatment, and were surveyed again at 6 months and 1 year. Of the 111 patients, 23 were positive again at 6 months, and 4 more at 1 year, despite further treatment in some villages during the year. In view of the length of the prepatent period, it is unlikely that any of the persons becoming positive at 6 months, or all of those becoming positive at 1 year, represent infections acquired after the original treatment.

Table 2 shows the number of recurrences during the first year. There is a statistically significant relation between recurrence rate and level of pretreatment MF. There is also a statistically significant difference between villages, probably attributable to variations in treatment scheduling discussed by Ciferri et al. (1969). The effects of pretreatment microfilarial density and of village are independent of each other.

There is also a statistically significant decline in recurrence from the first to the second half of the year. Table 3 shows the incidence of MF during the first year by time and by village. Note that inci-

Table 3. Recurrences by time and village among 111 treated original positives. Those with persistent MF one week after the start of treatment have been excluded

Village	Treatment schedule [a]	No. at risk	No. of incident cases	
			6 months	12 months
Amanave	B	31	9	1
Amouli	B	22	8	1
Aoa	A	16	4	1
Malaeloa	C	42	2	1
all villages	—	111	23	4

[a] Treatment schedules (as in Ciferri et al., 1969): A, 6 mg/kg daily for 6 days, a 1-year rest, and then 6 mg/kg daily for 6 days; B, 6 mg/kg daily for 6 days, a 6-month rest, and then 6mg/kg daily for 6 days; C, 6 mg/kg daily for 6 days, then 6 mg/kg once monthly for 6 months.

dence by time is partially confounded by the effects of the various treatment schedules used in different villages. In all villages incidence decreased in the second half of the year; the decline in incidence, therefore, seems to be independent of the differences between treatments. Incidence was significantly lower in Malaeloa during the entire year, but the striking part of this deficit occurred in the first 6 months, while the inhabitants of this village were receiving additional monthly doses of DEC. Recurrence may, therefore, be decreased by monthly treatment (Ciferri's Schedule C) during the time when recurrence rates would otherwise be highest. With the small number of cases available for analysis, no great differences in recurrence rate between treatment methods can be demonstrated after 6 months.

If one assumes an exponential decline in recurrence rate with time, the expected recurrence rate during the second year should be only about 1%, and is unlikely to exceed 5%. The true rate of decline of recurrence is probably greater than estimated, because some of the incidence noted at 1 year may be due to reinfection. Incidence in later periods greater than this 5% is probably due to some process other than recurrence.

NEW INFECTIONS

The terms " reinfection " or " new infection " describe infections by parasites acquired after treatment, in original positives and negatives. We shall follow Hairston's suggestion (personal communication, 1969) and refer to both processes as " new infections ". Infections acquired since treatment cannot become manifest until the passage of a time interval equivalent to the prepatent period. They can be estimated by measuring the incidence of microfilaraemia in successfully treated individuals beginning at least a year following treatment. By this time recurrence should have declined further from the latter half of the first year, and its confounding effect should be small. If new infections are observed, it is obvious that transmission is continuing.

Incidence of new infection was estimated in another sample from five villages of the Samoan study group. This sample consisted of all persons treated with 11–12 doses of DEC who had blood films taken before and at 1, 2, and 3 years after treatment, and were negative at the 1-year survey.

As this sample contains both original positives and original negatives, microfilaria status before treatment should be the first factor examined in relation to risk of new infection. There is good reason to expect original positives to represent a fraction of the population both exposed to infection and susceptible to microfilaraemia; conversely, original negatives would be biased towards lesser exposure and lesser susceptibility to microfilaraemia. These characteristics of life style and of physiological state should not be altered by drug therapy. One might therefore expect original positives to show a greater incidence of MF than original negatives. This is so; even with the majority of persistent MF and recurrence excluded by the sampling criteria, there is considerable excess incidence in original positives. Of 157 treated original positives negative at the 1-year survey, 49 (31%) became positive during the succeeding 2 years. Of 671 treated original negatives still negative at the 1-year survey, 19 (2.8%) became positive during the next 2 years. This difference is highly significant ($Z=7.6$, $P<10^{-8}$). Original positives (OPs) and negatives (ONs) are therefore dealt with separately in the following analyses.

Table 4 shows incidence of MF by age among original positives and original negatives. Although the

Table 4. Age-specific incidence of microfilaraemia in five Samoan villages during the second and third years following treatment

Age group	No. of negatives at risk: year 1	No. of incident cases: years 2 and 3	Incidence (%)
Original positives [a]			
0–9	31	8	26
10–19	42	15	36
20–29	20	5	25
30–39	21	4	19
⩾40	43	17	40
all OPs	157	49	31
Original negatives [b]			
0–9	278	7	2.5
10–19	174	5	2.8
20–29	60	2	3.3
30–39	54	2	3.6
⩾40	105	3	2.9
all ONs	671	19	2.8

[a] Not significant: $\chi^2 = 4.01$, 4 df, P = 0.4.
[b] Not significant: $\chi^2 = 0.30$, 4 df, P = 0.99.

original positives were older on the average than the original negatives, differences in incidence between the groups are not due to different age distributions. There is no significant difference in incidence with age within either original positives or original negatives. At all ages incidence of MF is greater in previous positives than in previous negatives.

Table 5 shows incidence of new infection by village. Differences in incidence by village among original positives are statistically significant, while those among original negatives are not. In all villages incidence is greater among original positives than among original negatives. Villages high in incidence among OPs tend to be high in incidence among ONs; those low in incidence among OPs tend to be low in incidence among ONs. Village differences thus explain part of the differences in incidence within both groups, but do not explain the larger difference in incidence between original positives and negatives. Comparison of Tables 2 and 5 fails to show any correlation of new infection rate in a village and earlier recurrence rates in that village.

Table 5. Incidence of microfilaraemia in five Samoan villages during the second and third years following treatment

Age group	No. of negatives at risk: year 1	No. of incident cases: years 2 and 3	Incidence (%)
Original positives [a]			
Amouli	22	4	18
Amanave	43	21	49
Malaeloa	51	18	35
Aoloau	25	3	12
Aoa	16	3	19
all OPs	157	49	31
Original negatives [b]			
Amouli	163	3	1.8
Amanave	165	9	5.5
Malaeloa	169	3	1.8
Aoloau	77	1	1.3
Aoa	97	3	3.1
all ONs	671	19	2.8

[a] Significant: $\chi^2 = 13.8$, 4 df, $P<0.01$.
[b] Not significant: $\chi^2 = 6.07$, 4 df, $P = 0.20$.

Table 6. Sex-specific incidence rates and male/female incidence ratios among original positives according to village of residence

Village	Incidence: years 2 and 3 (%)			Incidence ratio (M/F)
	All	Males	Females	
Amanave	49	60	33	1.8
Malaeloa	35	40	31	1.3
Aoa	19	14	22	0.6
Amouli	18	13	21	0.6
Aoloau	12	10	14	0.7

Among original positives, incidence in males was 37% and in females 26%; among original negatives, the comparable figures were 3.7% and 1.9%, respectively. Neither difference was statistically significant. An interesting interaction between the effects of sex and village was noted, however, and is shown in Table 6. Among original positives, the ratio of male to female incidence decreases along with overall incidence by village. This should be interpreted with caution because of the small sample size (157). The very small number of incident cases (19) among original negatives precludes this sort of analysis for this group.

The tabulation below indicates that differences in incidence between original positives and negatives are not all-or-none phenomena; there is a progressive increase in incidence of new infection according to original level of microfilaraemia. This difference is highly significant ($\chi^2 = 179.4$, 3 df, $P<0.0001$).

Pretreatment MF/20 mm³	*Incidence in years 2 & 3*
0	2.8%
1–10	14%
11–50	34%
⩾51	48%

Incidence of microfilaraemia among original positives was 17% in each of years 2 and 3. As some of the incidence in year 2 among OPs might have been attributable to recurrence, an adjustment was made for the most liberal estimate of residual recurrence (5%), reducing the year-2 incidence of reinfection to 12%. Even this drastic manœuvre failed to demonstrate any significant change in incidence of new infection in OPs between the two years ($Z = 1.2$, $P = 0.23$). Among original negatives, however, there is a clear increase in incidence of new infection

from 0.3% during year 2, to 2.5% during year 3 ($Z = 3.5$, $P = <0.001$).

These data show that new infections occurred in both original positives and original negatives in the pilot programme villages subsequent to mass treatment. Some determinants of risk are suggested by the figures for original positives and negatives taken separately. In both groups certain villages are associated with greater incidence. Incidence in males is higher overall than that in females, but at least among positives this effect seems restricted to high-risk villages. These findings suggest that within-group differences are probably environmental. Much larger differences between original positives and original negatives, though, indicate that major risk factors are not accounted for. Regardless of age, sex, place, or time, original positives invariably show higher incidence of new infection than original negatives. This seems to be a graded increase closely associated with original level of microfilaraemia. These differences between groups might be related to differences in susceptibility or in levels of exposure to infection in subgroups of the population. Such differences in susceptibility or relative exposure would not be changed by mass treatment with DEC.

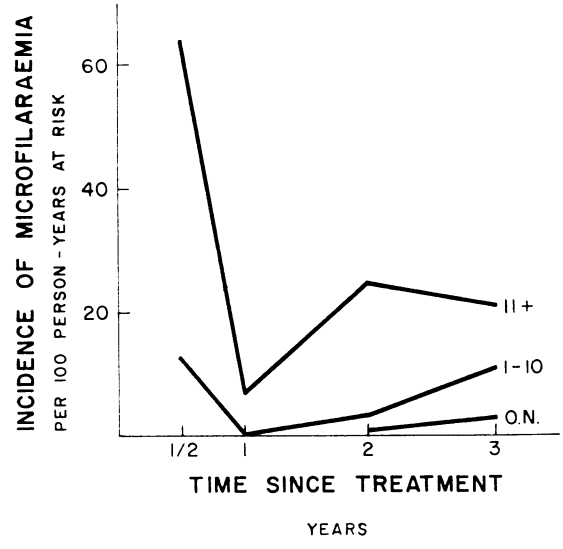

Fig. 1. Incidence of microfilaraemia by time since treatment and by level of original microfilaraemia. Because of different time-periods of measurement all rates have been reduced to person-years at risk.

DISCUSSION

Most previous work in filariasis control has been based on prevalence data from cross-sectional studies at various points in time. This report demonstrates the utility of incidence statistics derived from longitudinal observations in judging the effects of mass treatment programmes. Three phenomena formerly considered together as treatment failure can be examined separately.

Persistent microfilaraemia has been adequately discussed in the past (Cifferi & Kessel, 1967). At the dosage level of DEC used in this study, it appears to be related mainly to original microfilarial density.

Recurrence and new infection can be distinguished best by time of occurrence. Fig. 1 shows composite curves of incidence by time and by original level of microfilaraemia. The high points at the left represent almost exclusively recurrence; those at the right, almost exclusively new infection. The low points at 1 year on all curves represent the overlap of both phenomena when recurrence has fallen nearly to zero and most infection acquired after treatment has not yet become patent. Both recurrence and new infection contribute substantially to apparent treatment failures.

Recurrence is primarily a function of original level of microfilaraemia and of treatment scheduling. Recurrence can be minimized by monthly treatment during the first 6 months, although monthly treatment may not be worth the additional cost in time and personnel, as reductions in recurrence rate within the first year are not matched by corresponding reductions in new infection in subsequent years. The reasons for this are not clear.

New infections pose a more important long-range problem, as by the time of the year-3 survey, the reservoir of carriers of microfilaraemia contains almost 4 new infections for each persistent or recurrent case. There is about a twofold difference in risk of new infection according to village, associated with a slight difference in risk by sex. These figures point towards differing environmental circumstances favouring transmission. There is at the same time a tenfold difference in risk between original positives and negatives. This is not a dichotomous situation, but rather a continuous increase in risk proportional to original level of microfilaraemia. These findings raise new questions.

The findings of differential incidence by village associated predominantly with males is consistent with the hypothesis of Jachowski & Otto (1952) that

transmission occurs predominantly in plantations and in the bush. However, profound changes have taken place in the economy of American Samoa since this work, and in particular most men now spend little time in the plantations, but work outside the village environment for cash (Ramalingam, 1968). According to the hypothesis of Jachowski & Otto, therefore, incidence should be shifting to women and older men who continue to work in the plantation and bush environments. This is not apparent in the pilot programme data. It is possible that transmission occurs in other sites in the new work environments.

A further question is the large and consistent association of persistence, recurrence, and new infection with the level of pretreatment microfilaraemia. This association may, in accordance with the law of parsimony, be due to a single underlying mechanism, that of differential susceptibility in the population, or it may be the result of multiple factors, including differential exposure by occupation, housing, and life-style. In any case the highest incidence of microfilaraemia apparent after treatment occurs in previously infected individuals. This would indicate that the reversible catalytic models proposed by Hairston & Jachowski (1968) must be further refined to take into account the unequal risk of filarial infection in the different groups.

These factors determining susceptibility or exposure should be identified if eradication of filariasis is contemplated. Eradication requires that transmission be brought below a critical transmission level, at which the infection will die out without further control measures. This point is discussed by Hairston & Jachowski (1968). Our data indicate that effective transmission, as assessed by incidence, is not randomly distributed in the population. An eradication programme designed to reduce incidence below a predetermined critical level within an entire village may thus allow transmission considerably in excess of the critical level to continue in subgroups at high risk within the village. In this high-risk subset of the population the infection could be maintained indefinitely, and the eradication programme would fail in its objective.

These findings are of some interest to control programmes now in progress. The rationale behind mass treatment programmes has been somewhat as follows: mass treatment of the population will increase the rate of reversion, so that fewer positives are available to infect mosquitos; this will decrease the number of infective bites received by individuals in the population, and decrease the numbers of new cases. It is often overlooked that these changes in reversion rate may be only temporary. Given the same environmental circumstances favouring transmission, it is possible that the infection will return to its former level of endemicity as soon as mass treatment ceases. This is illustrated quite clearly by the rising incidence rates in this study that began a year after treatment. Successful control programmes should plan to maintain control pressures through environmental control or drug treatment over long periods of time, unless there is evidence that transmission has been reduced below the critical level. Original positives experience the majority of infections acquired after treatment. In view of this, environmental studies and control measures should focus on living areas and work activities of this group. In addition, it might be worth while to arrange special drug treatment for this group over and above that given to the general population.

RÉSUMÉ

ÉCHECS THÉRAPEUTIQUES DANS LES PROGRAMMES DE TRAITEMENT DE MASSE DE LA FILARIOSE

Les statistiques sur la prévalence de la filariose ne permettent pas une analyse correcte du problème des échecs thérapeutiques. Aussi les auteurs ont-ils réexaminé les données recueillies pendant les trois premières années du programme pilote de traitement de masse dans les Samoa américaines sous l'angle des statistiques relatives à l'incidence. Ils décrivent ainsi trois processus distincts habituellement groupés sous l'appellation « échecs thérapeutiques ».

Parmi 175 porteurs de microfilaires traités par la diéthylcarbamazine à la dose de 6 mg/kg pendant 6 jours, 32% étaient positifs une semaine après le début du traitement. Cette « microfilarémie persistante » était significativement plus fréquente chez les sujets qui présentaient initialement une microfilarémie plus intense. Six mois et un an après le début du traitement, on a réexaminé 111 sujets chez qui on n'avait constaté aucune persistance de la microfilarémie. Bien que réalisés en période de prépatence normale de l'infection à *Wuchereria bancrofti*, ces examens ont montré que 24% de ces sujets apparemment traités avec succès étaient à nouveau porteurs de microfilaires. La majorité de ces cas de

« microfilarémie récurrente » ont été décelés dans les 6 mois suivant le début du traitement. Le taux de récidive était significativement plus élevé parmi les malades fortement positifs avant le traitement. On n'a enregistré qu'un très petit nombre de rechutes parmi la population d'un village traité mensuellement pendant les 6 premiers mois.

On a recherché l'incidence de la microfilarémie, 2 et 3 ans après le traitement, dans un groupe de 828 sujets traités et trouvés négatifs un an après le traitement, afin d'exclure toute possibilité de persistance ou de récurrence de la maladie. Le nombre des nouvelles infections a été 10 fois plus élevé (31 %) parmi les sujets positifs avant le traitement que parmi ceux qui n'hébergeaient à ce moment aucune microfilaire (2,8 %). On a noté des variations considérables de l'incidence suivant les villages et, dans une mesure moindre, suivant le sexe. En revanche, fait intéressant, elle était sensiblement identique dans tous les groupes d'âge.

Ces observations démontrent l'absence de répartition uniforme du risque d'infection au sein de la population. La raison en est peut-être certaines variations individuelles de la réceptivité ou des degrés différents d'exposition dus à des facteurs de comportement ou d'environnement. Cette hétérogénéité du risque implique la nécessité de recourir à des modèles mathématiques plus perfectionnés pour l'étude de l'épidémiologie de la filariose et d'accorder une attention accrue aux groupes particulièrement exposés lorsqu'on élabore les programmes de lutte ou d'éradication.

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