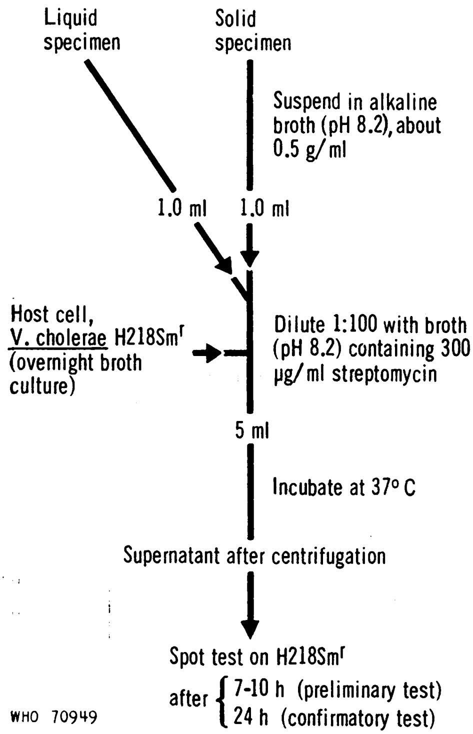
FIG. 1. SCHEME OF PHAGE-ENRICHMENT METHOD FOR ROUTINE USE



Committee (to be published), kappa-type phages were isolated from the bile along with El Tor vibrios. Moreover, numerous phage particles were isolated directly from one sample of duodenal fluid, while vibrios were detected only after enrichment culture. This might indicate that many vibrio cells persist in a spheroplast form in the hypertonic media of the bile. If this is so, long-term carriers would often excrete not the vibrio cells but only the kappa-type phages in stools. The present phage-enrichment method would be an excellent tool for detection of such long-term carriers.

On the other hand, the results of quantitation of vibrios and kappa-type phages in the stools of cholera patients during and after antimicrobial treatment (Joint Philippines-Japan-WHO Cholera Research Committee—to be published) showed that the phage was often detected even when the specimen was negative for vibrios, probably because of the non-susceptibility of phages to antimicrobials. Since the number of vibrios in the stools decreases rapidly on administration of antimicrobials, persons with mild cholera may pass a quarantine if they take antimicrobials before examination of the stools. However, the kappa-type phage would still be present in their stools as mentioned above and, therefore, the present phage-enrichment method will also be useful for detection of such cases during quarantine.

A Further Contribution to the Theory of Malaria Eradication

by Š. D. Moškovskij, *Chief, Protozoology Division, E. I. Marcinovskij Institute of Medical Parasitology and Tropical Medicine, Moscow, USSR*

In a recent report on the development of malaria eradication programmes the twofold question is asked why, in some cases or places, " [*a*] the transmission of malaria is not interrupted but [*b*] tends to become stabilized at a reduced level in spite of total coverage with the residual insecticide in properly conducted operations . . . " [a] It has been stated that there are still large areas where the methodology for the interruption of transmission is not yet known. To get the answer, from the theoretical point of view, a quantitative study of the dynamics of malaria eradication is required.[b, c]

The endemic level

The basic concept of the epidemiology of malaria is the endemic level,[d] which is not identical with the

[a] *Off. Rec. Wld Hlth Org.*, 1966, **151**, 78.

[b] Moškovskij, Š. D. (1950) [*Basic laws of the epidemiology of malaria*], Moscow.

[c] Moškovskij, Š. D. (1963) *The dynamics of malaria eradication.* In: *Proceedings of the Seventh International Congresses on Tropical Medicine and Malaria,* Rio de Janeiro, vol. 5, pp. 219-220.

[d] Ross, R. (1910) *The prevention of malaria*, London.

parasite, spleen or endemic index of Ross. The evaluation of the real figure of the endemic level, especially in highly malarious areas, requires special longitudinal studies.

The endemic level is the manifestation of a process basically consisting of the shift of persons. This shift represents a chain process which is maintained only if the gain in infected persons compensates the loss.

The parameters of this process are represented by two magnitudes (values): communicability and exhaustibility.[b,e] The first parameter (α) corresponds to the facility of the spread of the causative agent; it is measured in malaria as the mean number of infective bites distributed in the population and due to the presence of a case in a unit of time (e.g., a day). The second parameter (τ) corresponds to the mean probability of the disappearance (through recovery, death or departure) of an emerged case in a unit of time.

The paramount property of the endemic level is its self-regulation. Any disturbance of this level tends to its restoration as soon as the disturbing factor or factors are removed. Acquired immunity restraining the infectivity for the mosquito of the infected person and reciprocal interactions of the epidemiological process and demographic processes are additional regulating factors determining the endemic level.[f-j]

Corresponding to a greatly simplified but nevertheless very instructive model originating with Ross [d] and Martini,[k] the dependence of the endemic level M (expressed as the affected fraction of the population) on the epidemiological parameters may be represented by the equation $M = 1 - \frac{\tau}{\alpha}$.

If the ratio $\frac{\tau}{\alpha}$ becomes equal to unity, M becomes zero and this means that malaria should disappear. If the value of τ exceeds α, M acquires a negative value. The greater the absolute value of a negative M, the higher is the "epidemiological security" of the locality, i.e., the less likely is the conversion of the area into a focus of malaria.

[e] Moškovskij, Š. D. (1943) *Med. Parazit. (Mosk.)*, **12**, No. 4, p. 3.

[f] Macdonald, G. (1951) *Brit. med. Bull.* **8**, 33.

[g] Macdonald, G. (1955) *Proc. roy. Soc. Med.*, **48**, 295.

[h] Macdonald, G. (1956a) *Bull. Wld Hlth Org.*, **15**, 369-387.

[i] Macdonald, G. (1956b) *Bull. Wld Hlth Org.*, **15**, 613-626.

[j] Macdonald, G. (1957) *The epidemiology and control of malaria*, London.

[k] Martini, E. (1921) *Berechnungen und Beobachtungen zur Epidemiologie der Malaria*, Hamburg.

Classification of malarial foci

The planning of a malaria eradication programme begins by a differentiation of territory into zones according to: (*a*) the possibility of transmission of malaria and (*b*) the type of endemicity. Three main types of endemicity should be distinguished: *imaginary* (*quasi-endemicity*), *dependent*, *independent* (see Table 1).[l,m,n]

Quasi-foci are of importance only as places of temporary residence of cases (without local transmission), from where they may be imported into potential foci. Main measures are the detection of cases (always imported) and their radical treatment.

Presumed foci are characterized by negative values of M (see above) and should be differentiated according to the degree of epidemiological security. The lower this degree, the more strict must be the surveillance, to prevent the conversion of these foci into potential ones. This conversion requires changes in the values of the epidemiological parameters, caused by shifts in the interlinked factors and circumstances that determine the theoretical endemic level, M; i.e., the prevalence value that would ultimately be built up in the event of the import of malaria into a potential focus (into which the presumed focus would have been converted).

Potential foci (M positive) should be differentiated according to the level of endemicity which might be reached were cases imported in the absence of control measures.

Presumed and potential foci (in which no transmission occurs in spite of suitable natural conditions) are *probable foci.*

The targets of measures aiming at interruption of transmission are represented by the *actual foci*, in which transmission does occur. These foci may be ephemeral, permanent-dependent or permanent-independent.

Ephemeral foci (M negative) require stringent surveillance and interference, because they may supply cases to potential foci, thus converting the latter into actual foci. Ephemeral foci themselves may, with changing circumstances, become actual foci.

Dependent foci (M negative) are divided into groups according to the intensity of importation of

[l] Remennikova, V. M. & Aptekar, C. A. (1950) *Med. Parazit. (Mosk.)*, **19**, No. 4, p. 373.

[m] Beklemišev, V. N. (1959) *Med. Parazit. (Mosk.)*, **28**, 310.

[n] Beklemišev, V. N. (1960) *Bjull. mosk. Obšč. Ispit. Prir., Biol. Ser.*, **65**, No. 2, p. 41.

TABLE 1

CLASSIFICATION OF LOCALITIES ACCORDING TO THE DEGREE OF MALARIA TRANSMISSION [a]

1	Transmission impossible owing to natural conditions.
1.1	Transmission impossible. Malaria cases absent, or rare imported cases, or cases due to blood transfusion, may be found. *Malaria-free territory.*
1.2	Transmission impossible. Many cases are regularly imported. *Quasi-focus.*
2	Transmission possible.
2.1	Local conditions are *not sufficient* for the maintenance of malaria.
2.1.1	Transmission does not occur. Cases are absent. *Presumed focus.*
2.1.2	Transmission occurs.
2.1.2.1	Transmission episodic, owing to imported, sporadic, locally transmitted cases, or small outbreaks occur; these disappear even in absence of special measures. *Ephemeral focus.*
2.1.2.2.	Transmission continuous, although local conditions by themselves would not secure perpetuation of transmission; the focus exists owing to incessant replenishment of the sources of infection by importation. *Permanent-dependent focus.*
2.2	Local conditions are *sufficient* for the maintenance of malaria.
2.2.1	Transmission does not occur, owing to absence of sources of infection. *Potential focus.*
2.2.2	Regular transmission from indigenous sources secures self-dependence of the focus. *Permanent-independent focus.*

[a] 2.1.1 and 2.2.1 are *probab e foci.* 2.1.2.1. 2.1.2.2 and 2.2.2 are *actual foci.*

cases and the degree of local transmission. Main control measures—besides treatment of cases (both sick persons and so-called healthy carriers)—comprise the prevention of importation of cases and interruption of transmission.

Independent foci (*M* positive) represent the most important aspects of malaria eradication. The disappearance of these foci entails the self-exhaustion of the dependent, ephemeral and quasi-foci and prevents the conversion of potential foci into actual ones.

TABLE 2

VALUES OF v (SHOWING HOW MANY TIMES THE RATIO $\frac{\tau}{a}$ MUST BE INCREASED TO ATTAIN CONDITIONS NECESSARY FOR ERADICATION) FOR DIFFERENT THEORETICAL VALUES OF THE ENDEMIC LEVEL *M*

M (%)	*v*	*M* (%)	*v*
1	1.01	60	2.5
2	1.02	65	2.86
3	1.03	70	3.33
5	1.05	75	4
10	1.11	80	5
15	1.18	85	6.67
20	1.25	90	10
25	1.33	95	20
30	1.43	97	33.3
35	1.54	98	50
40	1.67	99	100
45	1.82	99.9	1 000
50	2	99.99	10 000

Independent foci are classified according to the prevalence values of malaria and to the loimopotential (intensity of transmission).[o] On these criteria depends the degree of changes (in the sum of epidemiological factors) required to achieve eradication. The dependence of the degree of change on the prevalence of malaria is represented in Table 2.

Table 2 shows that the size of changes necessary for malaria eradication increases very moderately until the prevalence reaches 75%-80%, but with the highest grades of holoendemicity the degree of restriction (of the factors determining the spread of malaria) required for the eradication of the disease becomes tremendous.

Such an increase concerning the areas where practically the whole population is affected is caused by the multiplicity of the infective mosquito bites inflicted on every person. This becomes clear from the analysis of the loimopotential. To infect 40% of the population with malaria 0.5 infective mosquito

[o] The term " loimopotential " expresses the average number of infective bites inflicted on a subject in a given focus per unit of time (see Moškovskij, Š.D. (1961) *J. Hyg. Epidem. (Praha)*, 5, 129; and page 124 of the volume cited in footnote *c* above).

bite per person per year will suffice. To infect 99.9% of the population (this corresponds roughly to a 2.5-fold increase in prevalence over 40%), the intensity of transmission (number of bites per person per year) must be 7—an increase of 14 times. This increase is still insignificant in comparison with the conditions in most heavily affected African areas, where the number of infective bites per night per person may be 100 or much more, thus making a loimopotential 10 000 times (or more) higher in comparison with an area where, for example, 40% of the population is affected.

Thus, besides the unfavourable economic conditions, nomadic mode of life, absence of medical staff, exophily of the vectors etc., the main difficulty in combating malaria in such areas lies first of all in the tremendous intensity of transmission.[p]

Main operational conclusions

For each independent focus of malaria there exists a critical level of restrictions to be imposed on the factors and circumstances determining the spread of the disease in order to cause a decline in the prevalence of malaria, tending to reach ultimately the interruption of transmission. This critical level is indicated by the value v in Table 2.

If the volume of changes brought about by a given set of control measures does not reach the required level, malaria eradication cannot be attained.

Thus, in areas with a low or even moderate endemic level, very small changes may bring about eradication. With higher endemic levels, reaching 80%-85%, an obvious reduction of the level will be attained only when a greater effort is made; the reduction being relatively smaller the higher the endemic level. But with the highest degrees of endemicity, even enormous changes in the situation may produce apparently little effect. In holoendemic areas almost no reduction of the prevalence is noted at the beginning in spite of the application of techniques which have brought about a complete interruption of transmission in areas with a lower endemic level.

This apparent inefficiency of the very intensively applied techniques in areas with the highest degree of endemicity often causes some pessimism and constitutes a psychological handicap to the continuation of efforts. But it should not do so. The absence of visible efficiency in such cases is the result of a state of epidemiological " hypersaturation ", i.e., of an enormous excess of the intensity of transmission in comparison with the percentage of the population affected. For example, with 86% of the population affected, this intensity corresponds to about 2 infective bites per person per year (according to Poisson's law), whereas in " hypersaturated " areas the number of infective bites per person may reach thousands for a similar period.

In these areas no further increase in the percentage of infected persons may take place in spite of even a tremendous increase in the loimopotential—this value being capable of unlimited increase, whereas the percentage of infected cannot, of course, exceed 100. Under such conditions, enormous efforts are necessary in order to relieve the population of the hundreds of infective bites per week or even per night, which exceed many times the number of bites necessary to produce 100% prevalence in the population. Only after the number of infective bites has been reduced to 2-3 per year will a reduction of the prevalence become visible. At the beginning this reduction will be a very small one—e.g., a drop from 100% only to 90% or 80%. But with this stage reached, successive, comparatively small further increases in the changes of the situation may bring about much greater reduction of the prevalence of malaria until eradication is ultimately achieved.

This schematic picture is, of course, too simplified. It does not take into account the difficulties caused by the increase of the fraction of non-immunes in the population, nor by the increase in live-births and decrease in the death-rate of children (owing to the decline of malaria), which bring about an increase of the number of efficient sources of infection.

These handicaps may also be overcome with appropriate increase and diversification of the measures applied. What is important is the rational explanation of the apparent absence of efficiency at the beginning of the work. A reasonable explanation of the seeming uselessness of the efforts is the best remedy against pessimism.

To show that the work is efficient even in the early stages the dynamics of the loimopotential must be followed up. We may find 10-fold to 20-fold or even higher degrees of reduction in the number of infective bites before any sensible drop in the percentage infected can be detected, and this will be the best proof that we are approaching the goal.

A very important way out for the most difficult conditions is opened by the *principle of multiplying effects*.[b,q] This principle is that effects arising from

[p] Pampana, E. J. (1963) *A textbook of malaria eradication*, London.

[q] Moškovskij, Š. D. (1944) *Med. Parazit. (Mosk.)*, 13, No. 2, p. 3.

the action we exert on different components entering (mathematically speaking) the epidemiological parameters as multiplicands (factors) are multiplied. Therefore a decrease of, say, 2, 5 and 8 times respectively in three factors promoting the transmission decreases the value of the whole parameter α by their product and not by their sum (i.e., not by $2+5+8=15$ times, but by $2\times5\times8=80$ times).

Some components enter the parameter as squares or higher powers. Thus, if we decrease the accessibility of man for the mosquito by 5 times (for instance, by increasing, through zooprophylaxis, the proportion of mosquitos biting cattle from 0.85 to 0.97, which decreases the proportion feeding on man from 15% to 3%), increase the mortality of the female mosquito per gonotrophic cycle by 4 times, and decrease the period of infectivity (for the mosquito) of the infected person by 10 times, then (with, for example, 3 gonotrophic cycles necessary for the maturation of sporozoites), the resulting decrease in the first parameter (α) will be $5^2\times4^3\times10=16\,000$-fold. This decrease is quite sufficient for interruption of transmission in most highly endemic areas.

This may be the answer, both theoretically and practically, to the first half of the question mentioned at the beginning of this paper.

Another aspect of the question exists, and this concerns mostly technical points that must be studied in detail in each area.

The second half of the question is as follows—why does the continuation of the efforts which have reduced the endemicity level from, let us say, 80% to 30% not bring about any further drop of the prevalence in some conditions? Why does this 30% level become stabilized in spite of the continuation of spraying (even in combination with other techniques), whereas in another area with an initial 30% endemicity level, a less efficient effort resulted in quick eradication? Or, to put it the other way round, why in the 80% area was the effect of the system applied more drastic at the beginning of the campaign, and why did it then gradually decline, finally stopping at the 30% prevalence level ?

The answer is as follows. Our techniques do not lose their efficiency with decreasing endemicity level. The gradual flattening of the curve is caused by the approaching of the new level of endemicity which corresponds to the newly established ratio of the epidemiological parameters. The changes in the situation brought about by the system of measures are, in this case, sufficient to reduce the 80% level to 30% and to maintain it there. Were our efforts (or their results—in the case of measures possessing a durable after-effect, as, for instance, construction of draining systems) discontinued, the endemic level would grow again and reach the initial figure of 80%. Thus the continued effort is necessary to withstand the self-regulation of the endemic level, which tends to return to the initial figure. In an area with an initial 30% endemic level, even a much smaller size of changes in the situation is sufficient to reduce the endemic level to zero, i.e., to interrupt transmission.

In consulting Table 2 we see that, for the reduction of the endemic level to 30% in an area with an initial 80% level, the conventional figure for the size of changes would be 3.57 (5.0-1.43), where 1.43 is the change required for the interruption of transmission in a 30% endemic level area. In order to achieve the interruption of transmission in the former area, the changes (measuring 3.57 units) having brought about the drop from 80% to 30% must be increased by 1.43 conventional units.