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Population studies of *Plasmodium vivax*. 2. Distribution of manifestations in foci of tertian malaria

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The authors investigate a mathematical model based on the theory they proposed in a previous publication. The model fits field data collected in re-established foci of tertian malaria. The patterns of distribution of manifestations of tertian malaria among the population may readily be explained on the basis of the theory of polymorphism of sporozoites.

Lysenko et al. (*5*) suggested a theory to explain the phenomenon of latency in *Plasmodium vivax*, based on the assumption that the early and late manifestations are provoked by different types of sporozoites: tachysporozoites (TS) and bradysporozoites (BS), respectively. A comparison is made here between predictions based on this theory and field data.

MATHEMATICAL MODEL OF DISTRIBUTION OF MANIFESTATIONS IN A FOCUS

The following model is based on the theory suggested by Lysenko et al. (*5*) and deals with a focus of malaria with a relatively short period of intensive transmission (about three months or less).

The following assumptions have been made:

1. Early attacks (i.e., manifestations occurring during the season of transmission or later, up to December of the year of the infection) are caused by TS, while late manifestations (i.e., those occurring during the year following the season of transmission) are caused by BS.

2. TS and BS are transmitted independently.

3. Every effective act of infection can be recorded separately (effective acts are those acts that are followed by manifestations).

Let:

t be the mean number of effective infections by TS per person under risk per epidemiological year;

b be the mean number of effective infections by BS per person under risk per epidemiological year;

$m = t + b$ be the mean number of manifestations per person under risk per epidemiological year; from assumption 3, the number of manifestations equals the number of effective acts of infection, thus m is also the force of infection (*6*);

$e = 2.718\ldots$;

$T_0, T_1, \ldots T_n$ be the proportions of persons under risk who have been effectively infected 0,1 ... n times by TS, respectively;

$B_0, B_1, \ldots B_n$ be the proportions of persons under risk who have been effectively infected 0,1 ... n times by BS, respectively;

$M_0, M_1, \ldots M_n$ be the proportions of persons under risk who have been effectively infected 0,1 ... n times by TS and/or BS, respectively.

The proportion of cases is $1-M_0$. The proportion of relapses is equal to the proportion of cases with more than one manifestation, i.e., $1-M_0-M_1$. The proportion of patients with relapses out of the proportion infected is:

$$z = (1-M_0-M_1) / (1-M_0) = 1-M_1 / (1-M_0) \quad (1)$$

The mean number of relapses per person under risk is equal to the difference between the mean number of manifestations per person under risk and the proportion of cases, i.e., $m - (1-M_0)$. The mean number of relapses per infected person is:

$$y = (m-(1-M_0)) / (1-M_0) = m/(1-M_0)-1 \quad (2)$$

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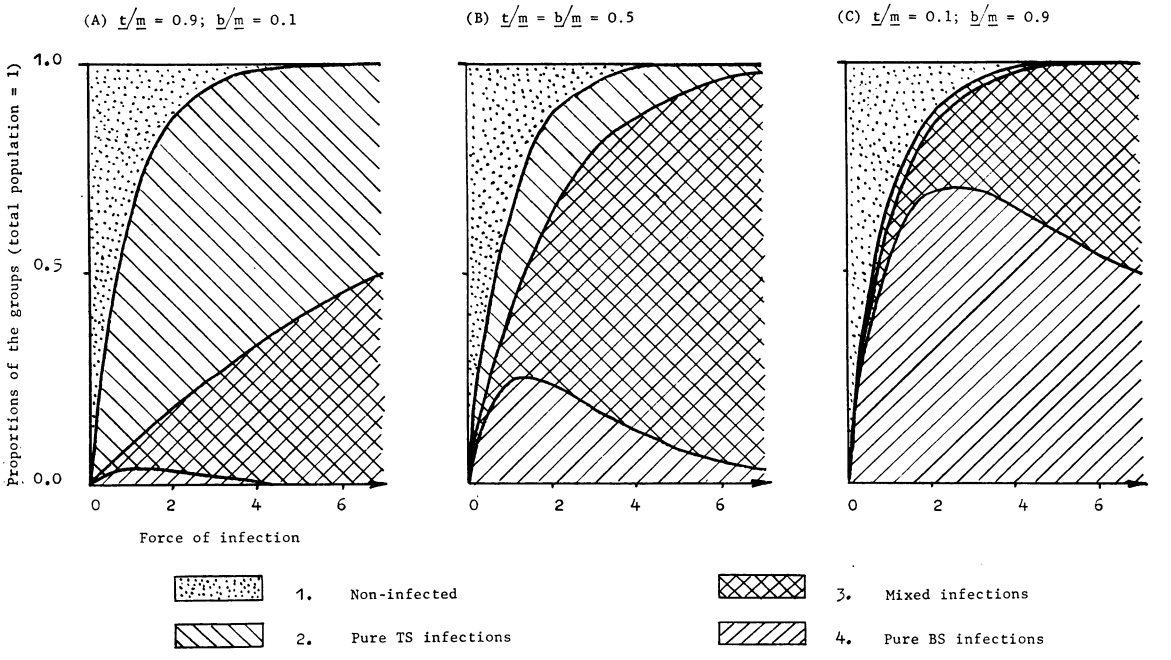

Fig. 1. Four population groups in foci of tertian malaria.

The distribution of manifestations among the population should be considered in two different situations: firstly, where acts of infection are evenly distributed in the population; and secondly, where acts of infection are clustered.

Equal risk of infection

In this case, several acts of infection by the same or different types of sporozoite are combined at random. The distribution of subjects by the number of manifestations will fit the Poisson distribution:

$$M_n = m^n e^{-m}/n! \quad (3.1)$$

$$T_n = t^n e^{-t}/n! \quad (3.2)$$

$$B_n = b^n e^{-b}/n! \quad (3.3)$$

The proportions of people who have not been infected by TS or BS are T_0 and B_0, while the proportions who have been infected are $1-T_0$ and $1-B_0$, respectively. The population of the focus may be subdivided into four groups:

Groups	*Proportions*
1. Non-infected	$T_0B_0 = e^{-m}$
2. Pure TS infections	$B_0(1-T_0) = e^{-bm}(1-e^{-tm})$
3. Mixed infections	$(1-T_0)(1-B_0) = (1-e^{-tm})(1-e^{-bm})$
4. Pure BS infections	$T_0(1-B_0) = e^{-tm}(1-e^{-bm})$
Total	1

The corresponding functions are presented in Fig. 1. As the force of infection (m) increases, the proportion of non-infected people decreases. The proportions of pure infections first increase and then decrease, due to the increase of mixed infections.

In epidemiological analysis, groups 2 and 3 are usually added and therefore the incidence of long incubation periods is greatly underestimated, even where there is an overwhelming prevalence of BS over TS (Fig. 1C). Fig. 1 may also be used to demonstrate the difference between natural and artificial infections: in natural infections, m is usually low and pure types of infection are frequent (the left sides of the graphs); in experimental infections, m is usually high and pure types of infection are nonexistent (the right sides of the graphs).

Individual combinations of sporozoites are designated by combinations of letters (T and B) and indices. The letters indicate the type of infection and the indices indicate the number of infections of the corresponding type contracted by a given person: thus, (T_i, B_j) designates the set of patients who simultaneously acquired i infections by TS and j infections by BS.

In the Poisson distribution model, the proportion of subjects with a given combination of infections may be obtained by multiplying the probabilities T_i

and B_j. For example, the proportion of people with two TS infections and one BS infection (from the clinical point of view, this will be a case of a short incubation period with one early and one late relapse) will be:

$$T_iB_j = T_2B_1 = (t^2e^{-t}/2)(be^{-b}) = bt^2e^{-m}/2, \text{ etc.} \quad (4)$$

The proportion of patients who have relapses may be obtained from equation 1, M_0 and M_1 being found from equation 3 ($M_0 = e^{-m}$; $M_1 = me^{-m}$):

$$z = 1-M_1/(1-M_0) = 1-me^{-m}/(1-e^{-m}) \quad (5)$$

As $m \to 0$, $z \to 0.5m$. If $m < 0.6$, $z \approx 0.5m$, the difference not exceeding 10%.

The mean number of relapses per infected person may be obtained from equation 2:

$$y = m/(1-M_0)-1 = m/(1-e^{-m})-1 \quad (6)$$

As $m \to 0$, $y \to 0.5m$. If $m < 0.6$, $y \approx 0.5m$, the difference not exceeding 10%. It is obvious that $z+y = m$.

Unequal risk of infection

Where cases were clustered, the negative binomial distribution model was used. This model proved to fit well the distributions of various parasites within host populations (*2*, *1*). The negative binomial distribution has two parameters: the mean of the distribution (m) and the measure of clustering (k). As $k \to \infty$, the clustering decreases and when $k = \infty$, the negative binomial distribution reduces to the Poisson distribution.

In the negative binomial distribution:

$$M_0 = (1+m/k)^{-k} \quad (7)$$

$$M_n = M_{n-1}(k+n-1)\,m/((k+m)\,n) \quad (8)$$

In particular,

$$M_1 = M_0km/(k+m) \quad (9)$$

As in the case of the Poisson distribution, the proportion of patients with relapses (z) and the mean number of relapses per case (y) may be obtained from equations 1 and 2, M_0 and M_1 being obtained from equations 7 and 9.

Proportions of subjects infected by a given combination of TS and BS cannot be calculated in the negative binomial distribution model by a simple multiplication of the probabilities T_i and B_j, as was done in the Poisson distribution model; however, they may be obtained as follows. A group of patients, each with n manifestations, may be subdivided into a number of subgroups: T_n, B_0; T_{n-1}, B_1; ... T_0, B_n. The frequency distribution of these subgroups can be fitted to the expansion of the binomial, $(t/m + b/m)^n$. For example, a group of patients, each of whom had three manifestations, may be presented as follows.

Designation of subgroup	T_3, B_0	T_2, B_1	T_1, B_2	T_0, B_3
Frequency of subgroup	$(t/m)^3$	$3(t/m)^2(b/m)$	$3(t/m)(b/m)^2$	$(b/m)^3$

These are the frequencies of individual combinations where the total number of the members of the group is 1. If the total number is M_n, each term in the expansion must be multiplied by M_n (obtained from equation 8).

OBSERVED DISTRIBUTION OF MANIFESTATIONS OF MALARIA IN FOCI

The distribution of manifestations of tertian malaria has been studied in four re-established foci of malaria in the Ažerbajdan SSR (*4*). In these foci, transmission took place during one summer. The next year, transmission was radically interrupted but cases of malaria continued to emerge.

Each manifestation was recorded separately. The manifestations that took place between June and November were designated as early ones and were

Table 1. Distribution of the cases of tertian malaria contracted during one epidemiological season

	Foci			
	A	B	C	D
No. of persons at risk	421	486	211	175
No. of cases	184	123	66	40
No. of manifestations:				
early	104	102	44	32
late	126	60	37	10
total	230	162	81	42
Distribution of persons at risk by number of manifestations:				
0	237	363	145	135
1	141	93	54	38
2	40	22	9	2
3	3	7	3	0
4	0	1	0	0
m	0.546	0.333	0.384	0.240
t	0.247	0.210	0.209	0.183
b	0.299	0.123	0.175	0.057
t/m	0.452	0.631	0.544	0.762
k	∞	1.12	∞	∞

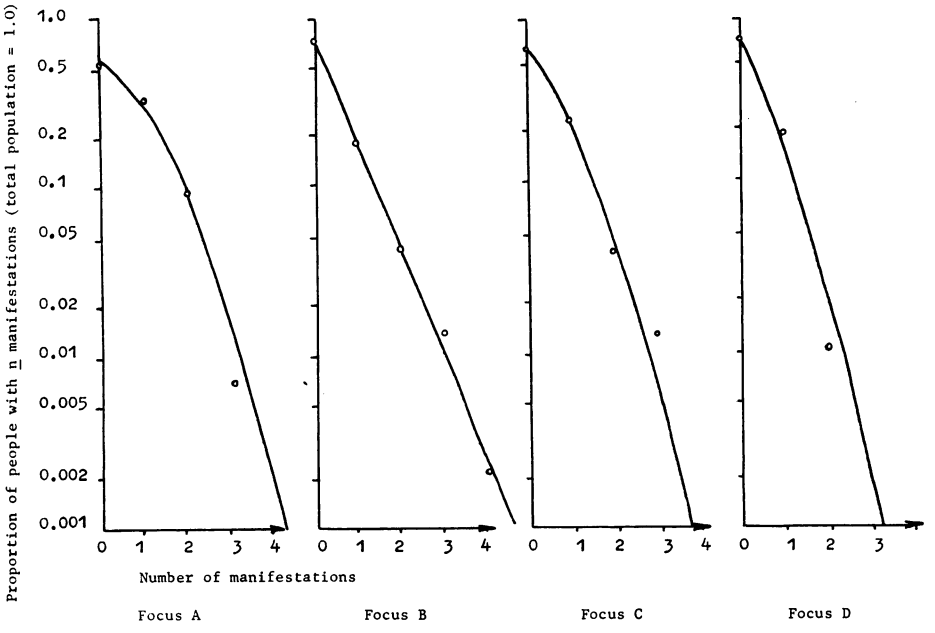

Fig. 2. Distribution of the population of four foci by the number of manifestations. Curves are theoretical distributions: Poisson distribution in foci A, C, and D; negative binomial distribution in focus B.

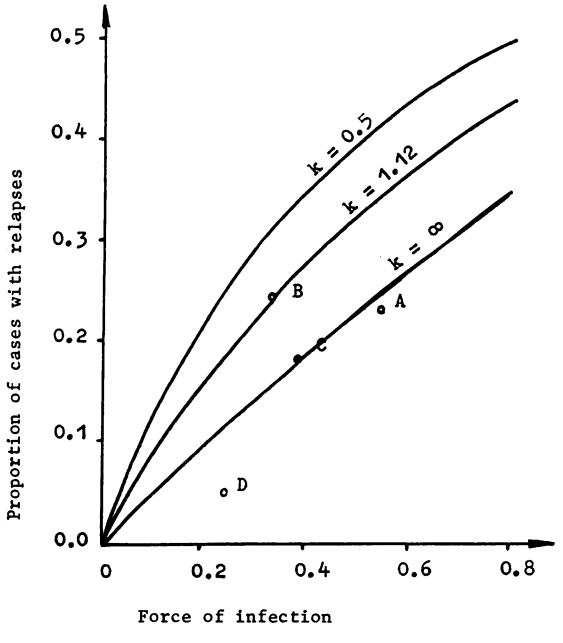

Fig. 3. The incidence of relapses and the force of infection. k = Parameter of clustering. Curves are the predicted values, points are the observed ones. Points A, C, D correspond to foci with an equal risk of infection ($k = \infty$); B corresponds to a focus where cases are clustered ($k = 1.12$).

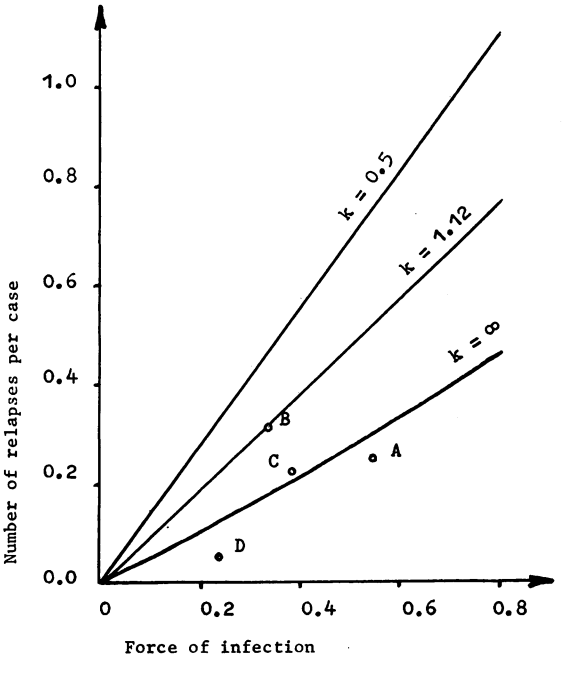

Fig. 4. The mean number of relapses per infected person and the force of infection. The designations are as in the Fig. 3.

Table 2. Observed and predicted number of cases of various categories in foci of tertian malaria

Category of case	Number of cases									
	Focus A		Focus B		Focus C		Focus D		Total	
	obs.	pred.	obs.	pred.	obs.	pred.	obs.	pred.	obs.	pred.
Total number of cases	184	177.2	123	122.9	66	67.3	40	37.3	413	404.7
Cases with short incubation period:										
total	91	92.2	90	85.0	40	39.7	30	29.2	251	246.1
with early relapses	13	10.9	11	14.2	4	4.0	2	2.8	30	31.9
with late relapses	29	23.8	21	15.8	11	6.4	0	1.7	61	47.7
Cases with long incubation period:										
total	93	85.0	33	37.9	26	27.6	10	8.1	162	158.6
with relapses	4	12.1	4	3.4	0	2.4	0	0.2	8	18.1
Total number of relapsing cases	43	44.0	30	29.7	12	12.1	2	4.3	87	90.1

Table 3. Observed and predicted number of relapses in foci of tertian malaria

Type of relapse	Number of relapses									
	Focus A		Focus B		Focus C		Focus D		Total	
	obs.	pred.	obs.	pred.	obs.	pred.	obs.	pred.	obs.	pred.
Early	13	11.8	12	16.9	4	4.3	2	2.8	31	35.8
Late	33	40.9	27	22.0	11	9.4	0	1.9	71	74.2
Total	46	52.7	39	38.9	15	13.7	2	4.7	102	110.0

ascribed to infection by TS. There were no manifestations during December and January. The second wave began in February and lasted until September; these manifestations were designated as late ones and were ascribed to infection by BS. The maxima of the incidence occurred in July and April. All these cases that emerged during a period of over one year were the result of infections during one, relatively short, epidemic season.

Two parameters were computed on the basis of field data: m, the force of infection, was obtained by dividing the number of manifestations by the number of persons at risk; t, the incidence of early manifestations, was obtained by dividing the number of early manifestations by the number of persons at risk. Both parameters varied considerably (Table 1).

The distributions of people at risk by the number of manifestations (Table 1) were then investigated. In three foci (A, C, D), the Poisson distribution fitted the observed data well (tested by the Kolmogorov test); in the fourth focus (B) the observed distribution was excellently fitted by the negative binomial distribution with $k = 1.12$ (Fig. 2). It is worth mentioning that in focus B there was an obvious clustering of the cases around the village.

The number of relapsing cases and the number of relapses correlated positively with the force of infection and were also linked to the parameter k. The observed data closely followed predictions (Fig. 3 and 4).

Considering only two parameters, m and t, and taking into account the type of the distribution, we computed the probabilities of different combinations of manifestations. The predicted values proved to be similar to the observed ones (Tables 2 and 3) although the basic information was very restricted.

CONCLUSIONS

It seems that the assumptions of the model fit the field data well. Proceeding from the theory considered in the first part of this paper (*5*), it has been

possible to describe the whole diversity of manifestations of tertian malaria in foci. The correlation between the relapse patterns and the force of infection that had been noted long ago (*7*, *8*, *3*) has now been given a theoretical grounding.

Thus, the theory of polymorphism of sporozoites facilitates the understanding of field data. Moreover, it seems that antimalaria activities in foci of tertian malaria should be seriously revised. Suggestions for such a revision will be presented in a later paper.

RÉSUMÉ

ÉTUDES DES POPULATIONS DE *PLASMODIUM VIVAX*. 2. LA DISTRIBUTION DES MANIFESTATIONS DU PALUDISME DANS DES FOYERS DE FIÈVRE TIERCE

Les auteurs envisagent un modèle mathématique qui décrit les distributions de manifestations du paludisme à *P. vivax* dans des foyers à transmission saisonnière. Ce modèle est fondé sur la théorie du polymorphisme génétique des sporozoïtes discutée dans la partie 1.[a] Le modèle est confronté avec les données obtenues lors d'une enquête épidémiologique dans quatre villages de la RSS d'Azerbaïdjan. Il est trouvé que le modèle satisfait aux observations épidémiologiques. Les distributions de cas selon le nombre de manifestations sont du type Poisson dans trois foyers et du type distribution négative binomiale dans un foyer. En partant seulement de deux paramètres, m (le nombre total de manifestations par habitant) et t (le nombre de manifestations précoces par habitant), on peut reconstruire toute la gamme de combinaisons qui ont eu lieu dans le foyer, c'est-à-dire calculer les effectifs des individus qui ont eu 0, 1, 2, ... n manifestations, le nombre de cas par catégorie (les cas à incubation courte et à incubation longue, les cas à rechutes précoces et tardives, etc.), le nombre de rechutes précoces et tardives, etc. Les auteurs estiment que les résultats obtenus apportent un argument d'ordre expérimental à la théorie du polymorphisme des sporozoïtes.

[a] *Voir* ce numéro, pages 541-549.

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