Relapse Pattern in *Plasmodium vivax*

Plasmodium vivax malaria constitutes 60–65% of total malaria cases in India (Sharma 1996). Although the infection is benign except for a few case reports of severe malaria. But the morbidity is high especially due to relapses which is characteristic of vivax malaria. Blood schizontocidal drugs are not effective against persistent hypnozoites of the parasite in the liver. Primaquine (8-aminoquinoline) is the only available drug active against hypnozoites of relapsing malaria parasites. Indian national drug policy (2002) recommended 600 mg chloroquine on Day 0 and primaquine 15 mg/day for five days (adult dose) as radical treatment for *P. vivax* infection against WHO recommended schedule of 14 days treatment with primaquine. But due to logistics and operational reasons and potential side-effects of primaquine, five days of primaquine treatment was followed by NVBDCP in India. As per the current national drug policy on malaria (2008) microscopically positive *Pv* cases should be treated with chloroquine in full therapeutic dose of 25 mg/kg body weight divided over 3 days. Primaquine should be given in doses of 0.25 mg/kg body weight daily for 14 days to prevent relapse except in those with G-6-PD deficiency, infants and pregnant women.

To evaluate the efficacy of different dose schedules of chloroquine and or primaquine, number of studies have been carried out in different geo-epidemiological zones of the country where this species of malaria parasite is predominant. The list of these studies is given chronologically in Table 11. Most of these studies revealed that five days treatment of primaquine was inadequate to prevent relapses and relapse rates were highly variable, ranging between 2 and 30% depending on the duration of follow-up of patients. Most important information obtained was that 70% of the patients never had a relapse after the primary infection without any primaquine treatment.

Among the relapse patients, approximately 60% had only one relapse, while 25% patients had two and 7% had three and remaining 6% had four or more relapses during one year follow-up. Lag month of relapses within one year revealed approximately 80% had relapses within 12 months and 10% had in the following year. Although the intervals between primary attack and first relapse ranged widely, the most common intervals were 1–2 and 8–9 lag months.

Various studies on *P. vivax* relapses revealed existence of polymorphic *P. vivax* populations in different zones of the country, characterized by three main types of incubation periods following primary attack. Studies revealed existence of both tropical and temperate zone types of *P. vivax* populations with distinct incubation periods and existence of

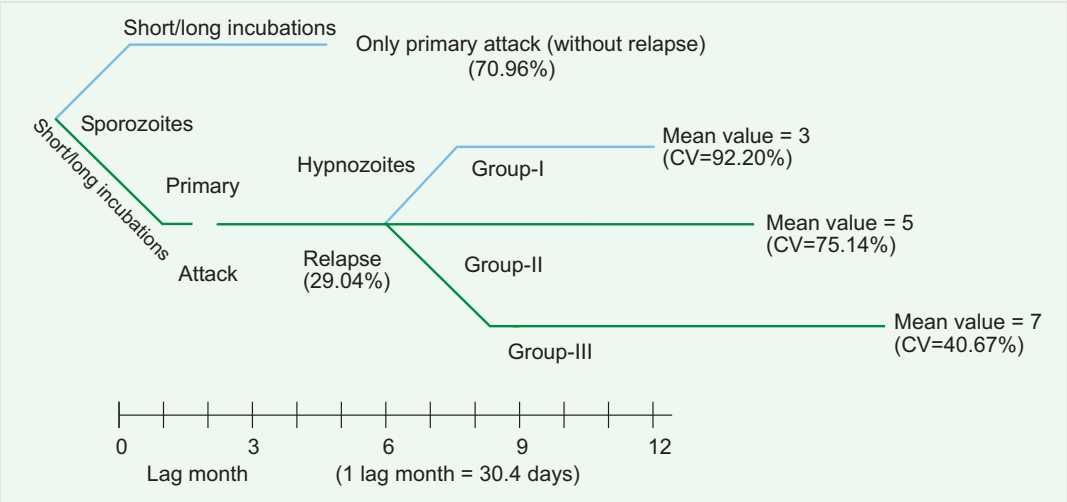

Fig. 14: Patterns of incubation interval in *P. vivax*. Group I = Primary attack between January and June (18%, n = 105); Group II = Primary attack between July and August (22.7%, n = 132); Group III = Primary attack between September and December (59.3%, n = 345); CV = Coefficient of variation (Source: Adak *et al* 1998)

Table 11. Relapse rates in *Plasmodium vivax* observed in different studies at NIMR

	No.*	Groups	Chloroquine	PQ**	Follow-up	Relapse rate %	Study site
Sinha *et al* 1989	725	1	900 mg over 2 days	Yes	395 days	6.9 (I relapse) 1.1 (II relapse) 0.27 (III relapse) 0.14 (IV relapse)	Hardwar (Uttarakhand)
Singh *et al* 1990	995	A (1987)	900 mg over 2 days	Yes	8 months	10.3 (I relapse) 0.01 (II relapse 0.002 (III relapse)	Mandla (M.P.)
	2500	B (1988)	900 mg over 2 days	No	8 months	8.9 (I relapse) 0.01 (II relapse) 0.002 (III relapse)	
Sharma *et al* 1990	1520	A (1984-88)	600 mg over 3 days	Yes	1 year (passive)	2.6	Kheda (Gujarat)
	264	B (1988)	1500 mg over 3 days	No		18.9	
Srivastava *et al* 1996	226	A	600 mg	No	1 year	28.3	Kheda
	173	B	600 mg	Yes		5.78	(Gujarat)
	136	C	600 mg+ 50 mg Pyrimethamine	No		27.7	
Adak *et al* 1998	316		900 mg over 2 days	No	5 years	44.3	Delhi
	487				4 years	30.2	
	497				3 years	26.2	
	524				2 years	28.4	
	669				1 year	23.3	
Valecha *et al* 2001	224	A	1500 mg over 3 days	No	1 year	40.1	Delhi
	220	B	1500 mg over 3 days	Yes	1 year	29.6	
	219	C	1500 mg over 3 days	Bulaquine†	1 year	26.8	
Adak *et al* 2001	224	A	1500 mg over 3 days	No	1 year	40.1	Delhi
	220	B	1500 mg over 3 days	Yes	1 year	29.6	
	219	C	1500 mg over 3 days	Bulaquine†	1 year	26.8	
Yadav *et al* 2002	723	A	1500 mg over 3 days	No	1 year	8.6	Sundargarh (Orissa)
	759	B	1500 mg over 3 days	Yes	1 year	6.5	

*Number of patients; **Primaquine 15 mg/day x 5 days; †New 8–aminoquinoline 25 mg/day × 5 days

subpopulations. The summary of relapse pattern derived from various studies is presented in Fig. 14.

Data from a double-blind randomized clinical drug trial were analysed to find the comparative responses of two antirelapse drugs, bulaquine and primaquine, against different forms of *P. vivax*. A one year follow-up study strongly suggested that the duration of pre-erythrocytic development of *P. vivax* is a polymorphic character, exhibited by two strains of hypnozoites responsible for early and late manifestations after the primary infection. Short-term relapses were significantly higher in the first half of the year than long-term relapses, and the reverse was true in the second half of the year. Clinical drug response data showed that the hypnozoites characterized for short-term relapse were not susceptible to either of the antirelapse drugs in the currently administered dose, whereas hypnozoites characterized for long incubation were significantly susceptible. However, there is no parasitological and clinical marker available at present which could be used to analyze the genetic diversity of the *P. vivax* population and correlate this with epidemiological finding. Therefore, there is a strong need for laboratory and field studies as well as the use of mathematical models to interpret the complex transmission dynamics of *P. vivax* so that appropriate control strategies, including chemotherapeutic measures can be devised. ❑