Comparative Studies On Response To 5-Day Treatment With Primaquine Of Indigenous & Imported Cases Of *P. vivax* in Nepal in 1974-76

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Attempts to find shortened regimes for radical treatment of *P. vivax* in India were undertaken in the early 1950s on the eve of inauguration of the malaria eradication campaign. The operational advantage of such schedules as compared to the standard 14-day treatment with primaquine were evident, especially during the final stages of attack and consolidation phases, when the radical treatment of every case was imperative. The results of field investigations undertaken by Indian malariologists (Jaswant Singh et al, 1953; 1954; Basavaraj, 1960) served as grounds for introduction of a 5-day treatment course with primaquine into the National Malaria Eradication Programme (NMEP) of India. According to the results of their observations made in Central India (Madhya Pradesh State and Delhi) and Southern India (Karnataka State), the relapse rate after 5-day treatment with primaquine did not exceed 6.0%. Such a low relapse rate after 5-day treatment of *P. vivax* cases was thought to be because of semi-immune status of population of India (A. P. Ray, 1980-personal communication).

The example of introduction of 5-day radical treatment for *P. vivax* cases in India in NMEP was followed later on by neighbouring countries with identical malaria situations, like Sri Lanka and Nepal. During the next few years, when the eradication campaigns in these countries made a remarkable progress, the question of evaluation of efficacy of 5-day treatment regimes did not arise.

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However, at the beginning of the 1970s the global malaria situation had deteriorated and a wave of "post-eradication malaria epidemics" (1979) was reported in many countries of the sub-tropical and tropical belts, including India and Nepal. Limited financial resources did not permit reintroduction of the complex of antimalaria measures, therefore only selective measures might be afforded by the countries in question in order to check the epidemics. Antimalarial drugs appeared to be the only tool to combat malaria at the earliest stages of the development of epidemics in India and Nepal, and in view of this the question of efficacy of 5-day treatment emerged again.

In 1973, the data on this subject were published by Sharma et al, and revealed the results of investigation in Madhya Pradesh State. According to their data, the relapse rate was 8.4%. Later, these results were confirmed by Roy et al (1977 ; 1979) who showed that a high efficacy of the 5-day treatment regimen occurred in Tamil Nadu State.

There had, however, been no accurate information on the subject in Nepal, though malariologists in that country estimated the local relapse rate to be no more than 10%, based on the ground of similarity of malaria epidemiology in Nepal and India. The results of analysis of data related to the 5-day treatment with primaquine of *P. vivax* from 1974 to 1976 in the central region of the Nepal Malaria Eradication Organization (NMEO) are discussed below.

I. Description of the area, materials and methods:

Nepal launched the malaria eradication programme in 1958. As a result of its successful implementation there were only 2000 cases a year reported by the beginning of the 1970s, as against hundreds of thousand of malaria cases and tens of thousands of deaths due to malaria during the pre-eradication era. By 1972 almost all malarious areas of Nepal had been brought under consolidation, and the process of integration of basic Health Services had started gradually.

The post eradication epidemics of malaria took place in Nepal in 1974, when about 15000 cases were reported. In 1975, the Government, augmenting its own resources with the financial support of some international organizations and bilateral agencies, reverted the programme back to the attack phase.

The antimalaria activities in the full swing of a classical malaria eradication programme are continuing in an area with population of 3.1 million. About 3.9 million people are protected by other antimalaria measures. On the whole, about 95% of the total population residing in malarious areas of the country are protected by antimalaria measures. The original malaria endemicity in Nepal varied between hypo-to hyper-endemicity, with local transmission being generally possible up to the height of 4000 ft. MSL.

As in any mountainous country, in Nepal there are a few easily identified epidemiological malaria belts (zones):

- 1) Cultivated plains (outer terai);
- 2) Forested terai
- 3) Inner terai
- 4) Hills
- 5) Himalayan mountains

There is no indigenous transmission of malaria in the last zone.

NMEO is operating from its Headquarters in Kathmandu through four regional offices situated in Eastern, Central, Western and Far Western Nepal. Observations have been made in central Region of NMEO in three malaria belts—outer terai, inner terai and hills; the forested terai belt is dwindling in size in the Central region because of intensive forest cutting, and is becoming like the outer terai; the mountain belt was not included for observations because there is no transmission. Some of the most important characteristics of the different epidemiological belts are given in the Table-1.

Post eradication malaria epidemics in Nepal were due to P. vivax, which constituted more than 80% total malaria cases. From 15% to 30% of total incidence comprised imported cases from India, brought to Nepal by nationals who had worked temporarily in India for periods ranging from a few weeks up to several months.

All P. vivax cases treated with 5-day regime of primaquine had been epidemiologically classified, and subjected to follow up during one calendar year on a once-a-month visit basis. 5-day radical treatment of P. vivax in Nepal consists of 1500 mgm. of chloroquine and 75 mgm. of primaquine (adult dose). In case of relapse, the course is repeated.

During the period of follow up, the patients were residing in areas where different antimalaria measures were being done, as follows:

- 1) One round of DDT spraying in month of May (2g./m^2) in outer terai and in the hills;
- 2) Three rounds of DDT spraying (1g./m^2) in the month of March, May and August in inner terai.

House to house visits were made on a once-a-month basis in the former area and once-in-two-weeks in the latter. Presumptive and radical treatment were given in all areas. On the whole, the possibility of reinfection was reduced, though it could not be completely ruled out. Because of this, every case of parasitemia among people treated with the 5-day regime was classified as "relapse case".

II Results:

1) Efficacy of 5-day treatment Schedule:

Altogether 4018 indigenous and 871 imported cases of P. vivax have been treated. The results of the treatment of indigenous cases is given in Table-2 and the imported cases in Table-3. On the whole, the relapse rate among indigenous cases was 4.1% as against 8.5% among imported cases. It was also observed, that the relapse rate among indigenous cases in the outer terai and in the hills was more or less the same (3.2% and 2.3% respectively), and almost half as much as in inner terai (5.9%). No significant difference in relapse rate was reported among imported cases irrespective of the place in which they had been detected (9.5% in the hills, 8.3% in inner terai and 7.1% in outer terai).

The cases of repeated relapses were reported among indigenous as well as among imported cases (0.3% and 2.3% respectively). However, no relapse have been reported among indigenous cases after administration of repeated course of 5-day treatment, while 3 patients among imported cases have developed relapse (0.3%).

2) Interval between treatment completed and relapse:

This interval varied from zone to zone and was 196 days in outer terai, 205 days in the hills and 239 days in inner terai. On the average, this period for indigenous case was 213 days (min. 30 days; max. 370 days), and for imported cases was 125 days (min. 25 days; max. 367 days).

3) Comparative relapse rate among the cases with different season of infection:

The results of these observations are given in Table-4. As may be seen from the Table, the patients among indigenous cases who acquired infection in the autumn months produced more relapses than the cases infected in any other season of the year. On the contrary no such a trend was observed among imported cases. It was also noticed, that the interval between treatment completed and onset of relapse among indigenous cases infected in autumn months was on average 242 days as against 125 days in winter, 130 days in spring and 192 days in summer. The same interval among imported cases was 130 days in winter; 116 days in spring, 161 days in summer and 116 days in autumn.

III. Discussion:

The results of longitudinal observations on efficacy of 5-day treatment with primaquine of indigenous and imported P. vivax cases in Nepal have revealed that the relapse rate was low-4.1% and 8.5% respectively. This may be considered as quite satisfactory from operational point of view. The degree of relapse rate among indigenous cases varied in different geographo-epidemiological malaria belts of Nepal, and was higher among imported cases from India. On the whole, comparing Nepal population of P. vivax to that of India in terms of response to 5-day treatment with primaquine, it may be concluded that the former is more sensitive to primaquine than the latter (table-5). From Table 5 it may be seen that not only is the relapse rate different in each stratum but even the seasonal pattern of relapse is different.

The relapse rate and the pattern of relapse among the cases brought by Nepalese from India are very much alike, as was observed by different Indian investigators. The results of our observations and those given by Sharma et al (1973) are similar.

Results obtained in Nepal support the earlier finding by Indian authors regarding the high operational efficacy of 5-day treatment with primaquine during the recent post-eradication epidemics of P. vivax. However, they are somewhat in disagreement with the concept that hyper-sensitivity to antimalarials of the local strains of parasites in the countries of the Indian sub-continent is related to semi-immune status of population. The observations in Nepal were made during the process of building up of immunity among the population and this immunity therefore could not be high. It seems that a more appropriate and logical explanation of the fact of good response to 5-day treatment with primaquine in India and Nepal lies in the intrinsic characteristics of the P. vivax population in this part of the world.

(for tables & references please turn over leaf)

Malaria Belt Of Central Region Of NMEO

TABLE-1

Malaria Belt	Popu-lation (000)	Orig-inal Ende-micity	Ann-ual Para-site Incidence (API) 1974	The Seas-son of Hig-hest Trans-mission	Mon- th Total No. of Cases	Malaria Vectors		Mean Win-ter Tempe-ratur		Mean Summer Temperature		Rain-fall (mm)	Rela-tive Hum-idity (%)	Density of Popu-lation per Sq. Km.	Migration of Population	
						Pro-ved	Sus-pect-ed.	Maxi-mum	Mini-mum	Maxi-mum	Mini-mum				Inte-ernal	Exte-ternal
OUTER TERAI	896	Hypo-	0.	May- Nov.	89.2	<u>A. annularis</u>	<u>A. culicifacies</u> <u>A. fluviatilis</u>	23°C	7°C	36°C	20°C	1400	60	189.6	Yes	Bihar & Uttar Pradesh
INNER TERA I	421	Hyper-	2.1	May- Nov.	93.3	<u>A. fluviatilis</u>	<u>A. culicifacies</u> <u>A. annularis</u>	23°C	6.5°C	34.5°C	18°C	2700	65	100.0	Yes	1 J U. P. & W. Bengal
HILLS AND HILLY VALLEYS	393	Hypo-	0.8	June- Oct.	80.7	<u>A. fluviatilis</u> <u>A. macularis</u>	1	20°C	7°C	31.5°C	17.6°C	1500	61	133.6	Yes	Assam, Nagaland Meghala- ya & Tripura

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TABLE-2

Month-Wise Distribution Of Indigenous Cases Of VIVAX
Malaria and Relapse Cases In Central Region Of NMEO

(Nepal) In 1974-1975

	Jan.	Feb.	March	Apr.	May	June	July	August	Sept.	Oct.	Nov.	Dec.	Total
<u>MALARIA BELT</u>													
HILLS	8	6	6	9	27	67	119	123	116	81	55	10	627*
	0	1	0	0	1	2	1	1	3	6	3	2	20**
INNER TERAI	21	9	9	36	155	231	237	211	478	251	118	46	1802
	2	0	0	2	6	7	5	3	50	22	8	1	106
OUTER TERAI	36	10	11	28	98	182	239	163	252	240	243	87	1589
	1	0	1	1	1	3	1	2	4	14	8	1	37
CENTRAL REGION	65	25	26	73	280	480	595	497	846	572	416	143	4018
NMEO	3	1	1	3	8	12	7	6	57	42	19	4	163

TABLE-3

Month-Wise Distribution Of Imported Cases Of VIVAX
Malaria and Relapse Cases In Central Region Of NMEO

(Nepal) In 1974-1975

	Jan.	Feb.	March	Apr.	May	June	July	Aug.	Sept.	Oct.	Nov.	Dec.	Total
<u>MALARIA BELT</u>													
HILLS	35	28	26	36	38	27	33	19	25	30	28	22	347*
	3	5	5	2	2	2	2	1	1	6	4	0	33**
INNER TERAI	27	25	16	24	40	20	21	26	32	31	22	29	313
	0	4	1	1	5	0	5	2	2	1	1	4	26
OUTER TERAI	9	8	6	6	17	30	23	9	18	21	29	26	211
	2	1	0	1	1	1	3	0	2	2	1	1	15
CENTRAL REGION	77	62	50	66	95	77	77	54	75	82	79	77	871
NMEO	5	10	6	4	8	3	10	3	5	9	6	5	74

* The figures in numerator - No. of vivax cases.

** The figures in denominator - No. of relapse cases.

TABLE-4

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Comparative Relapse Rate Of Indigenous And Imported
P. Vivax Cases Detected In Different Season
In Nepal Central Region Of NMEO
1974-1976

Malaria Belt	Winter (Dec.-Feb.)	Spring (March-May)	Summer (June-Aug.)	Autumn (Sep.-Nov.)	Remarks Statistically Significant difference.
Hills	12.5	2.4	1.3	4.8	Autumn Vs. Summer
Inner Terai	3.9	4.0	2.2	9.4	Autumn vs. Any other Season
Outer Terai	1.5	2.2	1.0	3.5	Autumn Vs. Any other Season
Central Region of NMEO	3.4	3.2	1.6	6.4	Autumn Vs. Any other Season
Imported Cases in CR	9.2	8.5	7.7	8.5	No difference

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TABLE-5

Comparative Data On Response To 6-Day Treatment With
Primaquine-P. Vivax Cases In India And Nepal

Author (s)	Place of Observation	No. of persons treated and followed up.	Duration of follow up (days)	Relapse Rate			Mean Interval between primary manifestation and first relapse (days)
				First Relapse	Second Relapse	Third Relapse	
Jaswant Singh et al 1953	Delhi	20	365-731	5.0	—	—	14
Jaswant Singh et al 1954	Madhya Pradesh	46	180-224	0.0	—	—	—
Basavaraj 160	Karnataka	563	365	6.0	—	—	168
Sharma et al 1973	Madhya Pradesh	130	365	8.4	0.8	—	123
Roy et al 1977	Tamil Nadu	6393	365	1.3	—	—	143
Roy et al 1979	Tamil Nadu	1684	365	0.0	—	—	—
Roy et al 1979	Tamil Nadu	124	365	8.1	—	—	170
NEPAL 1974-76							
Im- port- ed cases	Indigenous cases						
	Hills & Hilly Valleys	627	365	3.2	0.0	—	205
	Inner Terai	1802	365	5.9	0.4	—	239
	Outer Terai	1589	365	2.3	0.2	—	210
	Central Region of NMEO	4018	365	4.1	0.3	—	213
	Central Region of NMEO	871	365	8.5	2.3	0.3	125

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