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DENGUE IN KERALA: A CRITICAL REVIEW

Dengue is one of the most serious and fast emerging tropical diseases which in certain socio-ecological settings exacts disease burden (465,000 DALYs across the globe) that can only be paralleled with that of malaria[1]. Dengue, with its two severe clinical manifestations – dengue haemorrhagic fever (DHF) and dengue shock syndrome (DSS), poses an increasingly perilous situation due to lack of specific antiviral drugs or vaccine[2,3]. The dengue virus belongs to the family flaviviridae. It comprises four antigenically distinguishable serotypes (DEN-1, DEN-2, DEN-3, and DEN-4), transmitted generally through the bite of various day-feeding mosquitoes, belonging to subgenus Stegomyia. However, Aedes aegypti is the principal vector responsible for dengue transmission the world over. To a lesser extent, Ae. albopictus, popularly known as the Asian tiger mosquito, is also credited with a secondary role in disease transmission in certain south-east Asian countries[4,5]. Both these mosquitoes are capable to perpetuate dengue viruses in nature through vertical (trans-ovarial) transmission[6,7]. Dengue is an incosequential disease presenting initially with flu-like symptoms, but it can progress to fatal DHF and/or DSS. Ironically, immunity developed against a given virus serotype is limited to this only and does not provide cross-protection against any one of the other three serotypes, and upon contracting a second infection subsequently with a different serotype, a patient with a strain-specific immunity may stand a greater risk of developing dengue haemorrhagic fever.

World-wide nearly 2.5-3 billion people (40% of the global population) continue to live at constant risk of contracting infection, while 50 million cases and 24, 000 deaths are estimated to regularly occur annually in 100 endemic countries world-wide, including hospitalization of nearly 500,000 cases of which 90% are children. The southeast Asia region contributes 52% or 1.3 billion cases annually. India is one of the seven identified countries in the region regularly reporting incidences of DF/DHF outbreaks and seems to be heading to transform into a major hyperendemic niche for dengue infection in near future, with more and more newer areas being struck by the epidemic dengue. The first confirmed report of dengue infection in India dates back to 1940s and thereafter several states began to report the disease which mostly struck in epidemic proportion often inflicting heavy morbidity and mortality, both in urban and rural environments[8,9]. In Kerala cases of dengue with some deaths were reported in 1997 for the first time, albeit detection of DEN-1, DEN-2 and DEN-4 viruses in the human sera in Kerala[10]. Dengue antibodies had been detected in human sera from Kozhikode, Cannur,

Palakkad, Thrissur, Kottayam and Thiruvananthapuram districts as early as 1979[11]. Interestingly, available records show that of the two well known dengue vector species in India, only Ae. aegypti (L.) occurred in these seropositive districts, though without an evidence of its role in the disease transmission in Kerala state. In recent times DEN-2 and DEN-3 have been isolated from the vector mosquitoes and human blood sera, respectively[12,13]. Development of hyperendemicity (ie., multiple virus circulation in nature) in a short span of one decade, along with incrimination of Ae. albopictus, is indicative of the severity of dengue infection in Kerala which warrants a first hand review of the emerging disease under the changing climatic and anthropogenic impacts.

Kerala state has, in course of last couple of decades undergone an enormous change in respect of both its physiography/climate and risks of emergence or resurgence of several vector-borne diseases. While Japanese encephalitis and filariasis had been endemic with focal distribution along certain coastal districts, malaria incidence has been on the rise with more indigenous cases reported every year. Significantly Kerala, which remained virtually a terra incognito for dengue infection till mid-1990s, has been experiencing a string of widespread epidemics annually and has now attained hyperendemicity causing appearance of DHF and DSS cases as well[14]. The recent emergence of dengue fever in Kerala seems to have a definite correlation with the climatic change and the imposing anthropogenic stresses[15]. The present review highlights the status of dengue fever in Kerala in the light of factors which have forced a sylvatic mosquito like Ae.albopictus to seek its new breeding habitat near human habitation and facilitating transmission of dengue virus in a virtually non-immune population!

Physiography and Climate

Kerala, with a total area of 38,863 sq. km (urban 3365 sq. km and rural 35,498 sq. km), is one of the swmaller states of the country. It nevertheless harbours a population of 3,18,38,619 (males 15468664, females 16369995) with a very high population density of 819 persons per sq. km., that is nearly three times the national average. Shaped as a high vertical slope with an average breadth of 50 km, it is endowed with diversified climatic richness, with a pinch of hydrological concern as 41 of its 44 rivers originating in the Western Ghat empty into the Arabian sea in less than 48 hours after a rain. The state's lowland region, which accounts for 10% of the total area, runs along the coastline and embodies beaches, swamps and lagoons, besides backwaters, paddy fields and coconut plantations. Kerala's midland (42% of the total landmass) is primarily made up of valleys with undulating small hills and meandering passages. A variety of seasonal, annual and perennial crops are grown in its mainly lateritic soil. Of all these crops, cocoa and pineapple plantations are of tremendous significance as dengue vectors have been found to breed there[16]. The highland region (48% of the total state's area), with steep hills is rife with forests and small streams. Plantation crops like rubber, tea, coffee and cardamom are grown in this region.

The diversity of its geographical features has resulted in a corresponding diversity in climate. While the high ranges along the eastern border have a cool and bracing climate throughout the year, the plains, invariably merging coastally into Arabian sea along the western flank, are hot and humid. The average annual rainfall (3000 mm) is quite high compared to other Indian states – almost three times higher than that in Karnataka while twice than in Tamil Nadu. The state basically enjoys four types of climate, viz., winter, summer, southwest monsoon and northeast monsoon.

The winter season sets in during the month of December and continues till the end of February. During this season comparatively there is less rainfall, especially in the northern parts of the state. Winter is followed by the summer season. It starts in February and continues till May. Temperature is very high during this period. Occasional showers is a characteristic of this season. Kottayam district tucked in the Western Ghat ranges receives the highest rainfall during this season. The southwest monsoon, accounting for 60-65% of the total rainfall, begins either in the end of May or in the beginning of June and fades out by September. The northeast monsoon, commencing in October, contributes to 25-30% of the total rainfall. The coastal areas record a maximum temperature of 32°C. The interiors record a maximum of 37°C during summer. In the coastal area it is hot and humid during April-May while cool during December-January.

A careful analysis of epidemics in Kerala illustrates that dengue not only seemed to have an epicenter in Kottayam before spreading over to entire Kerala, most of the cases had erupted in the mountainous and sylvan environs of the Western Ghat ranges on the south-western

edge of the peninsular India facing Arabian sea coast in Kerala of which it covers nearly 90% of the total landmass. The Western Ghat ranges receive variable amount of rainfall from both the southwest (May - July) and the northeast monsoon (September - November), and is characterized with the Shola forest punctuated with man-grown extensive plantations of rubber (Hevea brasiliensis), cocoa (Theobroma cacao), coconut (Cocos nucifera) and pineapple (Ananas comosus).

Centre for Research in Medical Entomology (CRME), Madurai carried out studies in Kottayam, Idukki and Ernakulam, besides the coastal Thrissur and Thiruvananthapuram districts – all of which have had epidemics during past few years (Fig.1). This region is fairly humid and warm throughout the year with the relative humidity and temperature varying between 70-90% and 22-34.5 °C, respectively. The annual precipitation is high reaching up to 3000 mm, with the maximum number of rainy days (18 – 21 rainy days/ month) being in May to August.

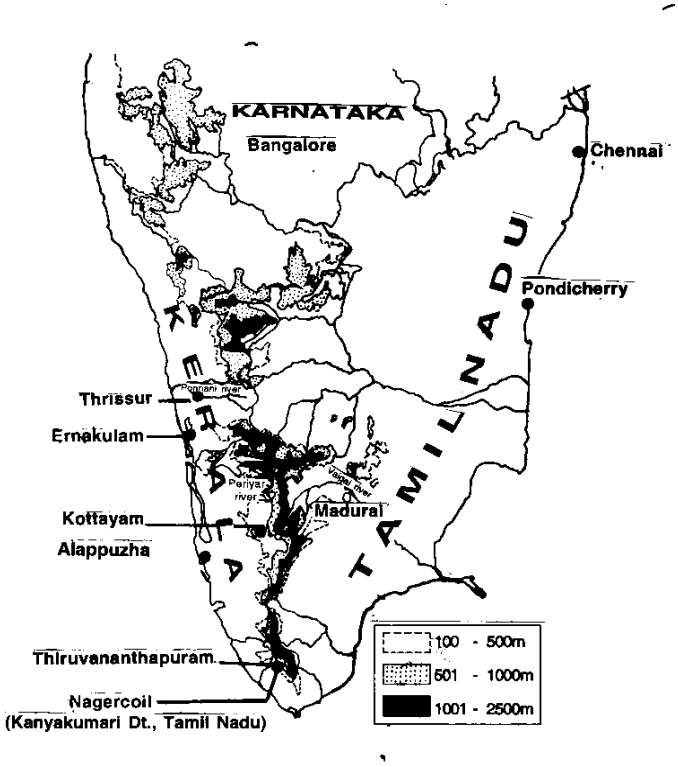

Fig.1 Peninsular India showing sites of investigation into dengue epidemic in Kerala and Tamil Nadu States.

(Note: The sprawling Western Ghat region, shown in dark and shaded areas, bracing the two states as well as harbouring the most severeliy epidemic struck sites).

Anthropocentric Activities: Change in Climate and Agriculture Versus Denguegenic Conditions

Anthropogenic impacts have brought about a discernible vicissitude in Kerala's forest cover, agricultural practices, traditional water harvesting, demography, urbanization and human mobility. It would be hard to believe that Kerala experienced a drought in 2003, with the average annual rainfall dipping to an all-time low of 2000 mm!

Although Kerala, which enjoys high rainfall, it still gets no more than 50-60 l. of water for domestic use per person daily. Water allowance per capita has depleted miserably in past few years. The Kerala state has an estimated 77.35 billion cubic meters (BCM) of fresh water, but nearly 40% of the resources are lost as run off, meaning only 42 BCM of water being available for the whole populace though the state requires a minimum of 49.70 BCM annually for various indispensably vital activities such as irrigation, domestic use, industries and others miscellaneous use. This shortage has lead people to resort to exploiting ground water so severely that the water table in several districts has gone alarmingly low. The water scarcity also induces people to store water in a mélange of containers like pitchers, cement tanks, etc. as long as possible.

A cadence in both ambient temperature and relative humidity is considered highly supportive to a wide dissemination of the dengue vector in time and space. There are evidences to prove a decline in rainfall, on one hand, and a marginal yet perceptible rise in ambient temperature, on the other. Since 1980 Kerala has suffered seven years of deficient rainfall and another five years below normal rainfall. An analysis of the southwest monsoon since 1998 shows that except Thiruvananthapuram in 2001, all districts have been receiving highly deficient rainfall in most years (Table I). Kerala had 2270 mm rainfall in 2003, still about 33% lesser than the average. It was amongst the few states in India declared drought-hit during 2003. It is noteworthy that since 1999 the annual rainfall has never touched the average value of 3107 mm; on an average, annual rainfall has dropped by 15-20% (Table II). The southwest monsoon has been particularly poor and in 2002 and 2003 it was deficient by as much as 33.3 and 26.4%, respectively. The year 2003 was further impoverished due to failure of northeast monsoon, with no area getting any rain during January-March. A close observation of rainfall data in various districts since 1900 shows that

Table I. Percentage deviation in southwest monsoon rainfall in all the 14 districts of Kerala compared to 1998 (Source: India Meteorological Department).

Districts	1999	2000	2001	2002	2003
Alappuzha	-27	-14	-16	-39	-33
Ernakulam	-35	-19	3	-33	-31
Idukki	-32	-17	-13	-38	-38
Kannur	-20	-24	-20	-30	-10
Kasargode	-23	-24	-3	-36	-22
Kollam	-24	6	-3	-38	-31
Kottayam	-37	-24	-16	-44	-33
Kozhikode	-31	-31	-33	-42	-33
Malappuram	-23	-29	-24	-45	-33
Palakkad	-27	-18	-27	-39	-43
Pathanamthitta	-16	-15	-13	-47	-34
Thiruvananthapuram	-22	-6	39	-57	-37
Thrissur	-34	-36	-28	-42	-39
Wayanad	-23	-1	-25	-34	-35

the number of rainy days in Kerala has dropped drastically. A discernible climatic cadence in Kerala is possibly linked with the atmospheric El Nino phenomenon which characterizes monsoon-related vagaries.

Soil in Kerala can retain water only for a maximum of three months. Unless it is replenished periodically through precipitation many parts of the state are subject to acute water shortage. For decades the marshy lands and wetlands, which recharge ground water and help retaining soil moisture, have been reclaimed for constructing houses and setting up industrial units including coconut and other plantations.

Forest, which help in orographic or convectional rainfall (i.e., rain in hill during evening), play an integral role in holding soil together and retaining rainwater, but large scale deforestation has been occurring in the state since 1970s, mostly with a view to planting cash crops like rubber plantation. Kerala had an estimated forest cover of 44.45% in 1900 which, according to the recent satellite images, had reduced to 14.7% in 1983 and to a pathetic 9% at present.

Kerala originally had a total cropped area spanning over 2 million hectares, with paddy as the major crop covering about 35% of this area, followed by coconut

Table II. District-wise average monthly rainfall in Kerala, 2001 (mm).

District	Jan	Feb	Mar	Apr	May	Jun	July	Aug	Sep	Oct	Nov	Dec	Annual
Thiruvanan-thapurum	2.9	10.1	17.8	63.1	124.6	265.4	221.4	122.6	401.2	227.6	308.2	115.2	1880.1
Kollam	1.3	4.6	75.6	155.4	229.9	365.1	431.2	269.1	311.4	432.2	265.1	110.4	2651.3
Pathanamthitta	0.0	13.4	87.8	80.3	246.2	310.5	654.4	401.3	419.8	456.0	376.8	106.3	3152.8
Alappuzha	2.1	2.7	67.2	94.7	156.7	465.7	702.9	425.7	477.4	362.9	256.4	161.8	3176.2
Kottayam	1.0	0.0	40.1	113.8	206.3	466.4	706.9	462.2	359.7	369.1	297.1	128.0	3150.6
Idukki	3.9	0.0	59.3	146.1	175.9	406.4	1111.8	713.9	345.6	357.4	438.5	147.9	3906.7
Ernakulam	5.8	1.0	48.0	86.3	130.1	550.6	942.6	471.8	415.4	329.0	377.2	141.7	3499.5
Thrissur	0.0	0.0	0.7	6.9	85.1	700.7	946.1	545.4	315.3	213.9	217.9	74.3	3106.3
Palakkad	0.0	14.1	36.8	30.8	125.1	337.3	813.9	380.2	149.3	215.9	283.1	26.7	2413.8
Malappuram	3.5	0.0	19.6	29.0	111.8	561.0	1173.9	575.7	246.0	317.4	363.1	52.4	3453.4
Kozhikode	1.6	0.0	9.5	1.0	67.1	1084.0	1495.7	728.7	158.4	207.4	238.4	62.7	4054.5
Wayanad	7.0	7.3	46.3	58.7	156.1	504.3	873.3	572.3	174.5	267.6	198.3	49.1	2914.8
Kannur	0.1	0.0	8.0	9.9	54.6	923.0	1571.5	803.7	157.2	134.7	259.6	68.9	3982.2
Kasaragode	0.0	0.0	6.1	4.3	16.5	929.8	1545.1	815.4	128.4	92.6	127.9	57.5	3723.6

(21%) (Table III). By 1975 the paddy growing area reduced to 30% of the total cropped area, with only 0.881 million ha growing paddy. In 2003 the area under paddy cultivation nose-dived to a paltry 0.31 million ha. However, the coconut plantation sustained a good growth rate of 3% per annum through 1990s. It is noteworthy that, along with coconut, rubber plantation has de novo supported breeding of dengue vector, *Ae. albopictus*[17]. At present while rubber plantations occupy the largest land area in Kerala, paddy fields have reduced and reclaimed largely for construction of human habitation[18].

Table. III. Population and land use in Kerala state[18]

Crops	Cropped area (1000 ha)		% increase or decrease
	1957	2003	
Rice	767	311	- 40.54
Coconut	463	906	+ 195.68
Rubber	100	476	+ 476.00
Pepper	91	201	+ 220.87
Tapioca	214	110	- 51.40
Other crops	576	1018	+ 176.73
Total	2211	3022	+ 136.68

Dengue Incidence in Kerala

Cyclic dengue epidemics in Kerala state have been occurring since 2001, even though the first dengue report was brought on record from Kottayam district in 1997 with 14 cases and 4 deaths (Unpublished observation). This was followed by a more sever dengue outbreak implicating 67 cases (nearly 5-fold increase) and a toll of 13 human lives (3-fold increase) in 1998, again in the same district (Table IV). The years of 1999 and 2000 were virtually free from any dengue cases. However, soon in 2001, epidemic dengue resurged mainly in Kottayam, Idukki and Ernakulam reporting 70 cases, followed by 219 cases in 2002 with some deaths. The year 2003 experienced the severest epidemic till date yielding as many as 3546 confirmed cases (253-fold increase) and a toll of 68 human lives, spread for the first time all over the Kerala's fourteen districts (Table V). The occurrence of DHF and DSS was also clinically and serologically documented. In spite of this history of dengue-related malady during past few years, no mosquito species was ever incriminated with a dengue virus in nature in Kerala, which created a void in comprehending the disease epidemiology.

Table IV. Dengue cases in different districts in Kerala state between 1997 and 2003

Year	Cases	Proportionate increase (taking 1997 as base year)	Deaths
1997	14	-	4
1998	67	1: 4.8	13
1999	1	-	0
2000	0	-	0
2001	70	1: 5	1
2002	219	1:15.6	2
2003	3546	1: 253.3	68

Epidemiology of Dengue in Kerala

In view of a rather recent emergence of dengue infection in Kerala, the data on disease epidemiology are very scanty and inconclusive. During 2003, however, the dengue cases, which initially kept a low ebb, suddenly began to appear in large numbers from invariably all the fourteen districts soon after the southwest monsoon, reaching a maximum of 1337 in the month of July (Fig.2).

It can be judged from these observations that 75.5% of the total dengue cases in Kerala in 2003 occurred only during the southwest monsoon period when *Ae. albopictus* also prevailed in higher density and after that nine of the fourteen districts continued to yield dengue cases till the end of the year, with Thiruvananthapuram reporting the highest incidence of 789/3546 (22.2%). It is also noteworthy that 9 of the 14 districts, of which four are landlocked in the high ranges of the Western Ghat mountains, had reported dengue cases for the first time. However, all those districts (e.g., Kottayam, Idukki, Ernakulam, etc.) which had been reporting dengue earlier had shown an increase in the incidence.

Clinically dengue patients presented a wide spectrum of signs and symptoms, often overlapping with flu and other infections, including leptospirosis. However, during an investigation carried out in 2003, major symptoms elicited by DF cases included fever (100%), headache (85.9%), retero-orbital pain (47.4%), myalgia (77.2%) and joint pain or arthralgia (47.4%). The haemorrhagic patterns of the DHF cases were manifested as rashes (86.3%), gum bleeding (21.1%) and purpural/echymosses (5.3%), etc. Children below 15 yr of age were quite severely affected (19.3%), although majority of infection

Table V. District and month-wise dengue fever cases in Kerala during 2003

District	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec	Total
Thiruvanan-thapuram	22	29	18	6	3	70	252	152	71	87	47	32	789
Kollam	1	1	1	0	0	3	33	99	29	9	5	5	186
Pathanamthitta	1	0	0	0	1	10	94	40	4	0	10	6	166
Alappuzha	0	0	0	0	0	24	101	77	7	5	3	3	220
Kottayam	0	0	3	0	0	46	106	20	5	8	3	3	191
Idukki	0	0	0	0	0	29	141	37	10	6	1	2	226
Ernakulam	0	0	0	22	0	51	150	47	17	10	12	10	319
Thrissur	0	0	0	0	1	83	73	87	51	30	18	20	363
Palakkad	0	0	0	0	0	22	53	52	9	9	2	0	147
Malappuram	2	11	12	0	0	42	248	143	58	18	8	4	546
Kozhikode	0	0	0	0	0	47	13	1	5	0	1	3	69
W ayanad	0	0	0	0	0	2	10	7	10	12	4	3	49
Kannur	2	0	1	1	3	87	32	13	7	5	3	0	154
Kasargode	0	0	0	0	0	5	31	44	18	18	3	4	121
TOTAL	28	41	35	29	8	521	1337	819	301	217	120	90	3546

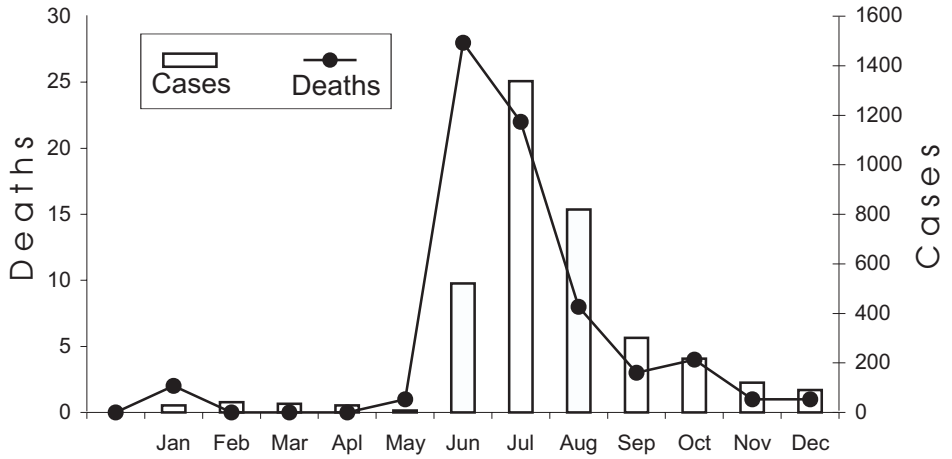

Fig. 2. Dengue cases and deaths in Kerala during 2003.

occurred in the active adult age group of 16-60 yrs (77.2%) with the geriatric group (>60 yrs) people being also vulnerable (3.5%). While a total of 52.64% patients exhibited haemorrhagic patterns of DHF, only 47.36% manifested signs and symptoms of the classical dengue fever. Five DHF cases showed multiple haemorrhagic manifestations with skin rashes being the most common. Rarely though, Gullain-Barre syndrome and acute necrotising myelitis of unknown aetiology were also reported to be associated with dengue infection[19].

Virus Detection and Isolation

Serologically, even though clinical cases had not appeared until late 1990s, the DEN-1 and DEN-4 viruses had been detected in 1970s from the human sera in a few districts of Kerala like Kozhikode, Kannur, Palakkad, Thrissur, Kottayam and Thiruvananthapuram[10,11,,20,21]. It was interesting that only Ae. aegypti without an instance of virus incrimination was recorded from all these districts covered under serological surveillance of local human

population and Ae. albopictus was conspicuously absent. During the 2003 outbreak, a total of 112 finger-pricked blood samples were collected from dengue suspected and/or confirmed cases. Of these, 74 (66.0%) sera originating from Pattanamthitta (22.9%), Kottayam (22.2%), Alleppy (Alappuzha) (24.3%), Ernakulam (6.7%) and Thiruvananthapuram (25.6%) were found positive in antigen capture MAC-ELISA. Using dengue positive human sera, the biological TOXO-IFA system was employed and DEN-3 (67%) was isolated from Kerala cases, implying introduction of a new dengue virus serotype. Additionally, a total of 37 human sera were tested by indigenously developed MAC-ELISA and 8 exhibited IgM antibodies against DEN-2 indicating recent dengue virus infection. These observations carry tremendous epidemiological significance from the viewpoint of evolving hyperendemicity.

Virus detection from a dengue vector in Kerala had been elusive until 2002. A long term investigation on both Ae. aegypti and Ae. albopictus in Kerala during 2002-2004 yielded a total of 240 pools (5173 adults) of Ae. albopictus comprising 112 pools (2456 adults) of males and 128 pools (2717 adult of which 413 were wild-caught) of females which were screened for the presence of dengue virus through ELISA. Of these, one pool consisting of 20 females, reared from the field-collected immatures from Mundakayam in Kottayam district, was positive for dengue virus, indicating the trans-ovarial mode of transmission. This phenomenon was further corroborated by a similar observation on Ae. albopictus in a nearby Nagercoil area (Kanyakumari district, Tamil Nadu) in the lower reaches of the Western Ghat ranges. Subsequently, during 2004, DEN-2 virus was finally isolated using the TOXO-IFA system and confirmed through ELISA from the two pools of wild caught Ae. albopictus female mosquitoes from Kottayam district, demonstrating with certainty the inevitable role of Ae. albopictus in the transmission of dengue in Kerala state. Ironically, so far Ae. aegypti has not been incriminated with a dengue virus in nature in Kerala.

Mosquito Fauna and Vectors of Dengue

A total of 9105 specimens belonging to 26 species under seven genera have been sampled in Kerala following various sampling methods. Among all the species, Ae. albopictus – the Asian tiger mosquito, was most dominant (69.7%), followed by Armigeres subalbatus (20.7%), Ae. aegypti (4.4%) and Culex uniformis (1.5%), with rest of the species accounting for less than 1% individually. Aedes aegypti was generally conspicuous by either a total absence or a very low density (Table VI).

Sampled species exhibited good degree of flexibility in breeding adaptability to various kinds of habitats. Aedes albopictus surpassed all species by exhibiting a wide spectrum of breeding preferences with a clear-cut predilection for coconut shells/plastic cups (79.7%) deployed in collecting latex from the rubber trees (Table VII). Aedes albopictus breeding in cocoa pods (Theobroma cacao) has been widespread in Western Ghat forest fringe areas and its significance has been duly emphasized in preserving the vector density during high monsoon times when the main breeding habitats such as the latex-collecting cups tethered along the main trunk of the rubber tree are rendered unsuitable for breeding due to latter being turned upside down or covered with polythene sheets to avoid water collection in cups[22]. Ae. albopictus maintained two peaks of high density correlating with the two monsoon seasons. This observation was considerably substantiated by both the container larval positivity and the adult landing index for Ae. albopictus. While the container larval positivity was as high as 64.1-73.8% in June and 80-84.3% in

Table VI. Mosquito species in different collections from Kerala during March 2002 - November 2003.

Species	Landing collection (55 Man-hours)	Immature collection (64 Man-hours)	Egg collection (338 Trap-days)	Total	%
Ae. (Stg) aegypti	0	368	36	404	4.44
Ae. (Stg) albopictus	683	2356	3305	6344	69.68
Ar. (Arm) subalbatus	60	1809	12	1881	20.66
Cx. (Lop) uniformis	0	137	0	137	1.5

Table VII. Breeding habitats of Ae.albopictus in Kerala

Breeding habitats	No. positive/surveyed	Percent positivity (To habitats)	Percent positivity(To total)
Natural			
Leaf axils (Pineapple)	14 / 36	38.9	2.2
Cocoa pods	12 / 18	66.7	1.9
Tree holes	5 / 7	71.4	0.8
Plant stumps (plaintain)	2 / 2	100	0.3
Total	33 / 63	52.4	5.3
Artificial			
Latex collecting cups	499 / 1093	45.7	79.7
coconut shells	45 / 89	50.6	7.2
Mud pots	8 / 21	38.1	1.3
Grinding stones	4 / 5	80.0	0.6
Flower pots	2 / 4	50.0	0.3
Cement cisterns	2 / 14	14.3	0.3
Total	560 / 1226	45.7	89.5
Discards			
Plastic containers	9 / 38	23.7	1.4
Tin containers	9 / 20	45.0	1.4
Tyres	7 / 10	70.0	1.1
Bottles	5 / 8	62.5	0.8
Abandoned shoes	3 / 3	100	0.5
Total	33 / 79	41.8	5.3

December, the adult landing index too was correspondingly high in June (7.2-11) and December (7.1-7.8), respectively.

High density of Ae. albopictus (Breteau Index about 20) compared to relatively very low BI for Ae. aegypti seemed to bear a direct impact on dengue transmission and dissemination since the highest cases seemingly arose during these two periods only; the more conspicuous peak of both cases and deaths being during the southwest monsoon.

Conclusions

Dengue is an enigmatic disease largely because it does not have a specific antidote nor a vaccine is available against this infection. In spite of the fact that in India dengue was first reported in 1940s, the first case of confirmed dengue infection from Kerala was recorded in 1997 only. Since 2001 occurrence of dengue increased in Kerala and outbreaks were reported repeatedly from most of the central and southern districts. DEN-1 and DEN-4 were detected in human

sera from Kozhikode, Kannur, Palakkad, Thrissur and Thiruvanthapuram districts, whereas DEN-2 alone was reported from Kottayam and Thrissur districts[23]. A wide distribution of DEN-2 virus was also emphasized in Kerala, without any evidence to vector incrimination[20], although Ae. aegypti was regularly sampled only along the sea coast. Characteristically no reference was made to the existence of Ae. albopictus in Kerala till 1980s, which is a competent vector for dengue viruses, and the presence of this species in association with Ae. aegypti increases the risk for emergence of dengue epidemics. Aedes albopictus has been incriminated with dengue virus in several south-east Asian countries[24]. Although the dengue virus serotype-4 has been earlier reported from Ae. albopictus in Asansol in West Bengal and Vellore in Tamil Nadu[25,26] the finding of Ae. albopictus carrying dengue virus in Kerala, that too in the absence Ae. aegypti, is reported for the first time. The present investigations have suggested that Ae. albopictus, prodigiously present in the Kerala's sylvan and mountainous Western Ghat ranges rife with rubber and cocoa plantations[17,27] – the likely epicenter of the epidemic dengue episodes in the state, is effectively transmitting dengue virus even in the absence or insignificant presence of the principal vector, Ae. aegypti, alluding towards its primary, rather than secondary role in disease transmission. It is, therefore, clear that there is a direct correlation between the preponderance of Ae. albopictus and the conflagration of dengue cases in Kerala. While circulation of multiple strains (hyperendemicity) in nature seems to be a comprehensible factor in conflagrating dengue outbreaks, discovery of DEN-3 virus in human sera in early 2003 and DEN-2 virus in Ae. albopictus soon after in 2004 lend a good support to the hypothesis that the dengue viruses are still in the process of dissemination and establishment across the length and width of the state. A constant occurrence of dengue cases from Kottayam district, adequately supported first by the detection of virus in Ae. albopictus in 2002 and subsequently its isolation from the same vector and site in 2004, allude towards a likely pathway of origin of dengue emergence in other neigbouring districts arising from Kottayam.

In view of these observations a clear parallelism can be viewed between the occurrence of dengue epidemic foci and the Ae. albopictus strongholds in Kerala[27], and the human-factor has obviously played an important role in dispersing the vector species in the hitherto uninvaded areas in the state and created conducive environment for man-Ae. albopictus contact[28]. Human behavior is often associated with the spatial and temporal distribution of Ae. albopictus in Kerala which has a tendency to displace Ae. aegypti from its habitats[29,30,31]. At least three human activity-related reasons can be attributed to the spread of Ae. albopictus far from its original sylvatic abode in the Western Ghat in yore to the coastal plains harbouring congested human settlements at present: (i) massive deforestation during past three decades that forced Ae. albopictus to come out of its natural abode, (ii) development of human settlements along forest fringe areas where mosquito frequently fed on human blood peridomestically, and (iii) its potential and likeness for transportation through different modes. Although, nothing is known at present about zoonosis in Kerala, it has been clearly demonstrated that dengue is a zoonotic disease of monkeys in Malaysia maintained by Ae. pseudoniveus/subniveus at canopy level[32]. Therefore, it would be interesting to know if monkey-based zoonotic reservoir would be occurring in the Western Ghat region abounding both in Ae. albopictus and different types of monkeys?

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This write-up has been contributed by Dr. B.K. Tyagi, Dy. Director (Sr. Grade) & Officer in-Charge, Mr.J. Hiriyan (Sr. Technical Officer), Dr. Philip Samuel (Research Scientist), Mr. S. C. Tewari (Research Officer) and Mr. R. Paramasivan (Sr. Research Officer), Centre for Research in Medical Entomology, Madurai.

COMMENTARY

Dengue virus diseases in Kerala

The comprehensive review of dengue virus infection and diseases in Kerala may be an eye opener for many, on several counts. The people of the state are known for near-universal literacy and pride in personal hygiene and environmental cleanliness. Kerala achieved population stabilization and <20 infant mortality rate more than two decades ago. Among all Indian states, Kerala enjoys the highest life expectancy. Is Kerala prone to environment-related infectious diseases – other than lymphatic filariasis that had existed there for a very long time?

In 1996, the state had a rude shock when an outbreak of Japanese encephalitis occurred, around the axis of Kottayam and Alappuzha districts. There were contemporaneous outbreaks of cholera in Alappuzha town and malaria in Kasargode. The state government obtained expert guidance, including that of the Director General of ICMR, and created the Kerala State Institute of Virology and Infectious Diseases, in Alappuzha, to serve as the nodal agency to investigate and intercept outbreaks, establish epidemiology expertise and training in the state and bring the best of diagnostic technology, particularly in virology, to serve the public health needs of the state. The immediate and direct benefits were the unraveling of leptospirosis as a major problem in the state, the detection of foci of spotted fever rickettsiosis and visceral leishmaniasis and documenting the endemic presence of malaria and cholera in the state. God's own country was indeed prone to many environment-related diseases, even in outbreaks.

Fortunately the efficient JE vector (Culicine mosquito) is not prevalent in Kerala and presumably for that reason there has not been any recurrence of outbreaks. However, sporadic cases have continued to occur and the smoldering presence of the virus suggests that we do not have a clear understanding of its eco-epidemiology. Strangely, JE virus had been isolated by CRME scientists from Kerala-caught Mansonioides mosquito.

In the 1950s and 60s students from Kerala coming to Madras (Chennai) or Vellore were prone to dengue fever the very next post-monsoon period. Keralites were non-immune whereas local people were immune. Earlier mosquito-surveys in Kerala had shown the absence of Aedes mosquitoes – egypti or albopictus. Indeed the entire western coastal region was free of Ae. egypti. In my medical school days we were told that this was a safety feature for India's freedom from yellow fever. Africa's eastern coast was also free from yellow fever. The review of dengue in Kerala by the CRME scientists depicts the story of its detection in Kerala and also that of Ae. albopictus. It was inevitable that dengue viruses, so widely prevalent in Tamil Nadu had to reach Kerala with its highly susceptible population and now, an abundance of vector mosquitoes.

Another eye-opener is the fact that all epidemiological and virological investigations of JE and dengue were conducted by scientists from CRME or the National Institute of Virology, Pune. To the best of my knowledge there is no virus culture or isolation facility within the state and the Alappuzha Institute of Virology and Infectious Diseases was not supported for this expertise. Kerala has every element necessary to be the leader and exemplar in Public Health among all states of India. It is the only state that had established a state-wide but district-as-unit disease surveillance system, which bridged the gap between public sector and private sector and is action-oriented. Let me encourage the state health system leadership to reinvigorate Public Health and apply science in the cause of disease prevention – including diseases due to old and recognized pathogens – like typhoid fever and rabies, as well as the resurgent or emerging diseases named above. As for leptospirosis and dengue haemorrhagic fever that we already have, they kill children and young adults, a situation that Kerala must not tolerate any longer. What is more ominous is that now the ecological conditions for yellow fever may be in place with susceptible population and efficient vectors. In Africa, yellow fever has become endemic in the eastern coastal region. If the virus reached here, it may become established, a situation we must anticipate and prevent, by constant monitoring of the vector breeding and density – and by keeping the vector population below the threshold necessary for virus transmission.

T Jacob John,
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ABSTRACTS

Some Research Projects Completed Recently

THE DEVELOPMENT OF A NEUROPSYCHOLOGICAL BATTERY FOR USE ON HINDI KNOWING CHILDREN.

The study was carried out to construct and develop a comprehensive neuropsychological battery in Hindi language and examine its efficacy in differentiating the children with brain damage from the normal children and find out if the neuropsychological battery would discriminate between children with lateralized brain damage. The battery consisted of 135 items spread over 10 basic scales: motor, tactile, visual, receptive speech, expressive speech, reading, writing, arithmetic, memory and intellectual processes. Four more scales were derived from these scales viz., pathognomonic, left hemisphere, right hemisphere and the 'total score' scale. The items retained in the battery were chosen following Luria's functional approach.

Three types of reliability studies were carried out: (i) test-retest; (ii) inter-rater; and (iii) the internal consistency reliability. Results indicated remarkably high coefficients for all types of reliability studies suggesting that the test scores were least affected by the time variance, examiner variance and also that the item sampling consistency was high.

Concurrent validity of the battery was established. The findings of the study revealed overall hit rates ranging from 67.45 to 93.83% on all the 14 variables. On the individual basis the total scale variable classified correctly was 96.67% of the normal group; 91.43% in the psychiatric group and 80.80% in the brain damaged group.

Using direction of difference between left hemisphere and right hemisphere scales, the battery had been successful in lateralizing nearly 88% of the left hemisphere damaged and 90% right hemisphere damaged patients.

It is concluded that the study has produced the comprehensive neuropsychological battery for Hindi knowing children which was proved to be a reliable and valid instrument for purposes of identification and lateralization of brain dysfunction in children. The battery is almost comparable or even superior to the tests or test batteries currently available. The battery offers comprehensiveness and accuracy of larger batteries in a two to two and half hour examination while exceeding single test in accuracy, comprehensiveness and usefulness in rehabilitation planning. Those working in the area of clinical child neuropsychology and in neurosciences may find it a useful test for demonstrating brain behaviour relationships. However, extensive additional research is necessary to establish fully the validity of the battery.

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CORRELATION OF APOLIPOPROTEIN E GENE POLYMORPHISM WITH DYSLIPIDEMIA AND BODY COMPOSITION IN NORTH INDIAN SUBJECTS: A CASE CONTROL STUDY.

The study was carried out on 73 non diabetic hyperlipidemic cases (triglycerides >250 mg% or total cholesterol >240 mg% or both and non diabetic) and 85 healthy controls matched for age and sex (non-diabetic, normolipidemic (triglycerides <200 mg% and total cholesterol <200mg% and non diabetic) to determine the influence of apolipoprotein E gene polymorphism with dislipidemia and body composition in Indian population.

Blood samples were drawn for blood sugar, lipid analysis and genomic DNA isolation. Body mass index (BMI) and waist hip ratio were measured in all the recruited individuals. Restriction isotyping for apo E gene from the genomic DNA of all recruited individual was done. Data thus obtained were recorded and statistically analyzed.

It was found that E4 form of apo E gene was significantly higher in hyperlipidimic individuals than in controls and hyperlipidimic individuals with E4 allele had higher total cholesterol and LDL cholesterol. Cases having E2 allele had higher triglycerides than their counterparts in E4 and E3 groups. The apo E polymorphism involves the coding region of apo E gene and results in alteration of gene product which inturn directly or indirectly affect the metabolic fate of lipoprotein particles. Phenotypic variation in apo E is a result of cys to arg interchanges at two positions (112 and 158) of amino acid sequence. Arg at both the positions in E4 enhances receptor

mediated clearance of LDL-c thereby down regulating LDL receptor resulting in increased TC and LDL-c. Apo E2 is metabolically impaired when compared to E3. This results in delayed catabolism of chylomicron and VLDL remnants into liver and decreased rate of LDL formation leads to up regulation of LDL receptor thereby leading to decreased LDL and increased triglycerides. High apo E4 frequency in hyperlipidemic individuals than controls signifies that E4 can act as risk factor for coronary artery disease.

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Publications:

1. Dwivedi, M., Luthra, K., Jailkhani, B.L. and Vikram, N.K. High prevalence of apolipoprotein E4 allele in hyperlipidemic Indian population; A case control study. Atherosclerosis (suppl) 4: 237, 2003.

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COLONIC MUCOSAL CHANGES IN PATIENTS WITH PORTAL HYPERTENSION – A CLINICO-HISTOPATHOLOGICAL STUDY

The study was conducted on 30 patients each of cirrhosis, extra hepatic portal vein obstruction and non cirrhotic portal fibrosis to find out the magnitude of macroscopic and microscopic colorectal lesions in patients with portal hypertension, assess the colonic histopathological changes and evaluate the correlation, if any of gastric mucosal changes (gastropathy) with colorectal changes (colopathy) and reveal the influence of aetiology of portal hypertension and stage of liver disease on occurrence of colopathy. Female patients with pregnancy and those with gastric/duodenal ulcers, carcinoma of the colon/recto-sigmoid region/oesophagus/stomach, inflammatory bowel disease and acute hepatic encephalopathy were excluded from the study.

Majority of patients were males (83%), cirrhosis (77%) was the most common cause for portal hypertension with post viral infection (44%) being the most common aetiology for cirrhosis. Colorectal changes were seen in a large number of patients (80%) and portal hypertensive gastropathy in 63% of patients.

Non-specific inflammatory changes, vascular ecstatic lesions and colo-rectal varices were the macroscopic changes most commonly found. The lesions themselves, although usually asymptomatic and clinically insignificant, are a potential source for acute or chronic lower gastrointestinal bleeding. Gastric mucosal changes and colonic lesions occurred together commonly. Prevalence of colorectal lesions increases in patients with portal hypertensive gastropathy, possibly reflecting more advanced portal hypertension. An increasing trend for the presence of colorectal lesions was seen in patients with cirrhosis, increasing severity of liver dysfunction and large oesophageal varices. Microscopic colonic changes were common, mild and representative of an underlying vasculopathy, which occurred irrespective of the presence or absence of macroscopic lesions.

The study was, thus able to highlight some of the common microscopic and macroscopic colonic changes seen in patients with portal hypertension.

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ICMR NEWS

The following meetings of various technical groups/committees of the Council were held:

Scientific Advisory Groups

Division of Publication & Information	March 30, 2006

Task Forces (TFs)/Expert Groups (EGs)/Steering Committee and Other Meetings

EG on Stroke and Surveillance Activities	March 1, 2006
EG on Cancer Atlas	March 3, 2006

Steering Committee of National Cancer Registry Programme	March 8, 2006
TF on Hypertensive Disorders of Pregnancy	March 17, 2006
TF on Leprosy	March 29, 2006
EG on Centre for Advanced Research on Liver Disease	April 4, 2006
TF on Comparison of Efficacy of DEC or Bioflavonoid Extract of Rutaccae aurantiae or Co-administration of Both in Reduction of Bancroftian Filarial Lymphoedema – A Multicentre Double Blind Randomized Clinical Trial	April 4, 2006
TF on Operational Feasibility and Impact of Co administration of Albandazole and DEC in Controlling Lymphatic Filariasis	April 4, 2006
EG on Centre for Advanced Research in Molecular Microbiology	April 5, 2006
TF on HIV and Tuberculosis	April 12, 2006
TF on North-East Projects	April 12, 2006
Sub-Committee on Double Fortified Salt	April 12 & 17, 2006
TF on Rotavirus	April 27, 2006

Project Review Committees (PRCs)/Project Review Groups (PRGs)

PRC on Biomedical Engineering	March 1, 2006
PRC on Oncology	March 2, 2006
PRG on Nutrition	March 8, 2006
PRG on Tribal Health	March 10-11, 2006
PRC on Experimental Medicine and Surgery, and Anaesthesia	March 13, 2006
PRC on Ophthalmology	March 21, 2006
PRC on Urology	March 23, 2006
PRC on Cardiovascular Diseases	April 24, 2006
PRC on Geriatrics	April 25, 2006
PRC on Mental Health	April 25, 2006

Participation of ICMR Scientists in Scientific Events

Dr. Vinod Joshi, Deputy Director, Desert Medicine Research Centre, Jodhpur, participated in meeting of Research Strengthening Group of Special Programme for Research and Training in Tropical Diseases (TDR) at Nairobi (March 6-7, 2006).

Dr. V.M. Katoch, Director, Central JALMA Institute for Leprosy and Other Mycobacterial Diseases, Agra, participated in the XXI NIMR Annual Joint Scientific Conference at Tanzania (March 7-9, 2006).

Dr. S.K. Bhattacharya, Director-in-Charge, National Institute of Cholera and Enteric Diseases (NICED), Kolkata and Additional Director-General, ICMR; Dr. Dipika Sur and Dr.T. Ramamurthy, Deputy Directors, NICED, Kolkata and Dr. Pradeep Das, Director, Rajendra Memorial Research Institute of Medical Sciences, Patna, participated in the XI Asian Conference on Diarrhoeal Diseases and Malnutrition at Bangkok (March 8-10, 2006). Dr. Bhattacharya also participated in the meeting of Board of Trustees and the Institute Support Council of the International Vaccine Institute at Seoul (April 10-12, 2006).

Dr. G. Narendran, Research Officer, Tuberculosis Research Centre (TRC), Chennai, participated in the NIMH/IAPAC International Conference on HIV Treatment Adherence at Jersey City (March 8-10, 2006).

Dr. A.K. Mukhopadhyaya, Senior Research Officer, NICED, Kolkata, participated in the discussion on Genetic Diversity of Helicobacter pylori and its Role in Pathogenesis, Disease Manifestation and Transmission at Dhaka (March 13-17, 2006).

Dr. P.R. Narayanan, Director, TRC, Chennai, participated in the Workshop on T-cell based Diagnosis of a Latent Tuberculosis Infection in Resource Limited Setting at Geneva (March 16-17, 2006). Dr. Narayanan and Dr. Soumya Swaminathan, Deputy Director (Sr. Grade), TRC, Chennai, participated in the Workshop on HIV Sequence Immunology and Vaccine Trial/Database at Colorado (March 27 – April 1, 2006).

Dr. H.N. Saiyed, Director, National Institute of Occupational Health (NIOH), Ahmedabad, participated in the VI meeting of the Standing Committee of the International Programme on Chemical Safety (IPCS) Programme Advisory Committee at Bangkok (March 21-23, 2006).

Dr. S.P. Tripathy, Deputy Director, National AIDS Research Institute (NARI), Pune, participated in the AIDS Clinical Trials Group Leadership Retreat at San Diego (March 21-23, 2006).

Dr. R.S. Paranjape, Director, NARI, pune, participated in the meeting on HIV Antiretroviral Drug Resistance in Asia at Hanoi (March 27-31, 2006).

Dr. P.K. Das, Director, Vector Control Research Centre (VCRC), Pondicherry, participated in the IV meeting of the Global Alliance to Eliminate Lymphatic Filariasis at Fiji (March 29-31, 2006). Dr. Das also participated in the III meeting of the South East Asia Regional Programme Review Group for Elimination of Lymphatic Filariasis at Jakarta (April 27-28, 2006).

Dr. J.M. Deshpande, Director, Enterovirus Research Centre, Mumbai, participated in the meeting of Working Group on Approaches to Improving Timeliness of Laboratory Results for Use in the Polio Eradication Initiative at Geneva (March 30-31, 2006).

Dr. Anjali Nag, Assistant Director, NIOH, Ahmedabad, participated in the VIII World Congress on Injury Prevention and Safety Promotion at Durban(April 2-5, 2006).

Dr. Nisha Mathew, Sr. Research Officer, VCRC, Pondicherry, participated in the International Conference on Structure based Drug Discovery at Whistler, British Columbia (April 4-9, 2006).

Dr. M.D. Gupte, Director, National Institute of Epidemiology, Chennai, participated in the meeting of the Global Forum on Leprosy Control and VIII WHO Technical Advisory Group Meeting for Leprosy at Aberdeen (April 18-21, 2006).

Dr. C.P. Batra, and Dr. P.K. Mittal, Assistant Directors, National Institute of Malaria Research (NIMR), Delhi, participated in the International Forum for Sustainable Management of Disease Vectors at Beijing (April 20-24, 2006).

Dr. C.P. Puri, Director, Dr. S.L. Chauhan, Assistant Director, and Dr. Jayanti Mania-Pramanik, Sr. Research Officer, National Institute for Research in Reproductive Health, Mumbai and Dr. Smita Joshi, Research Officer, NARI, Pune, participated in the Workshop on North-South International Collaboration in Microbicide Research (Microbicide 2006) at Cape Town (April 23-26, 2006).

Dr. R.R. Gangakhedkar, Assistant Director, NARI, Pune, participated in the WHO-UNFPA Strategic Partnership Programme Implementation Review and Planning Workshop for Countries of Intensified Focus at Bangkok (April 24-27, 2006).

Dr. Tapas Chakma, Assistant Director, Regional Medical Research Centre for Tribals, Jabalpur, participated in the LV Epidemic Intelligence Services Conference at Atlanta (April 24-28, 2006).

Dr. L. Singotomu, Deputy Director (Sr. Grade), National Institute of Nutrition, Hyderabad, participated in the International Meeting "Scanning 2006" at Washington, D.C. (April 25-27, 2006).

Dr. A.P. Dash, Director, Dr. Neena Valecha, Deputy Director and Mrs. Bina Srivastava , Lab. Technician, NIMR, Delhi and Dr. S.K. Sharma, Assistant Director and Officer-in-Charge, NIMR Field Station, Rourkela, participated in a meeting "A phase-II double blind parallel group randomized, dose ranging study assessing the antimalarial activity and safety of RBX 11160 administered for 7 days in patients with acute uncomplicated Plasmodium falciparum malaria at Basel (April 26-28, 2006).

Dr. Kamalesh Sarkar, Assistant Director, NICED, Kolkata, participated in the XVII International conference on Reduction of Drug related Harm at Vancouver (April 30- May 4, 2006).

Training Programmes/Fellowships

Dr. S. Ramesh Kumar, Research Officer, Tuberculosis Research Centre, Chennai, proceeded to Brown University, Rhode Island, USA under Fogarty International Training and Research Programme for 6 months w.e.f. March 30, 2006.

Dr. Amit Pal, Senior Research Officer, National Institute of Cholera and Enteric Diseases, Kolkata proceeded to Japan to avail training under JICA-NICED project on Prevention of Emerging Diarrhoeal Diseases Phase-II for 7 months w.e.f. March 1, 2006.

Report

Workshop on "Ethical Review for Protection of Human Participants involved in Research"

The Indian Council of Medical Research has been engaged in activities related to bioethics since the last decade. With the release of revised "Ethical Guidelines for Biomedical Research in Human Subjects" in 2000, it became imperative that the biomedical researchers in the country should be sensitized to realize that the human subjects involved in research should be adequately protected. In this connection, the Council received support for planning a curriculum for teaching bioethics to undergraduates, postgraduates, researchers and trainers. The Council also received support for centrally coordinated bioethics education for India which would test the above-mentioned curriculum in training programmes planned for different target groups. Subsequently, workshops are being organized in various parts of the country.

In this series a workshop was organized in New Delhi for Institutional Ethics Committee (IEC) Members (Chairman, Member Secretary and other members) across the country. The objective of the workshop is to sensitize the IEC members and increase awareness about ethical guidelines and regulations in India which should be meticulously followed during ethical review mechanism when human participants are involved in biomedical research. The participants included scientists and ethics committee members of ICMR institutes.

The topics covered in the workshop included:

- Introduction to Research Ethics: Historical Background, Ethical Principles, Animal Experimentation and ICMR Guidelines
- Institutional Ethics Committees: Management, Roles and Responsibilities
- Informed Consent: Content and Process
- Ethics Committees: Legalities and Lawyer's Perspective
- Ethical Issues in Clinical and Epidemiological Research including Standard of Care and Post Trial Benefits
- Risk Benefit Analysis
- Special Concerns: Inducement for Participation and Conflict of Interest
- Special Issues: Privacy and Confidentiality and Research on Stored Tissues
- Ethics of New Technologies: Genetics, Genomics, Assisted Reproductive Technology and Organ Transplantation

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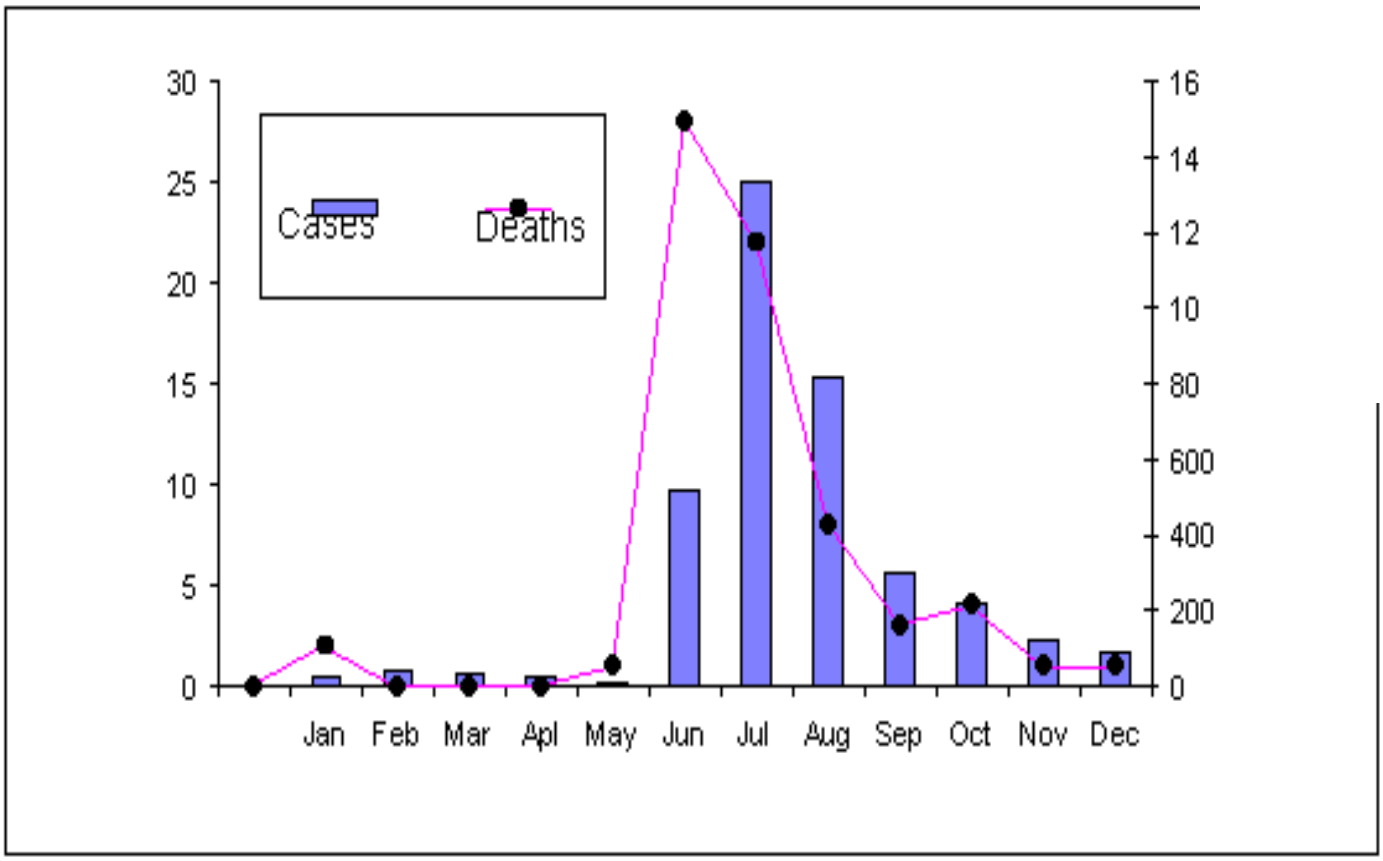
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