Review of literature
2. REVIEW OF LITERATURE

Anophelines are well known as the only vectors of human malaria all over the world wherever the disease occurs. What makes a species a vector and another not is a question, which has remained a curiosity of malariologists for a long time.

The mosquito fauna of the world comprises of 422 anopheline species, of which about 70 species have been known to have significant role in transmission of human malaria (Service, 1993). In India, there are 51 anopheline species and 7 subspecies or varieties out of which eight species are considered as the primary vectors of human plasmodia (Rao, 1984). They are An. culicifacies, An. stephensi, An. fluvialitis, An. minimus, An. philippinensis, An. sundaicus, An. annularis and An. dirus.

Natural infections with human plasmodia have also been found in An. aconitus, An. varuna, An. kochi, An. dthali, An. jeyporiensis, An. subpictus, An. vagus, An. maculatus, An. pallidus, and An. ramsayi. However, these are believed not to play any significant role in malaria transmission (Rao, 1984) owing to poor man-feeding habit.

2.1. Studies on vector susceptibility to human plasmodia

The physiological susceptibility of a mosquito species to parasite infection is an important quality that determines the potentiality of the mosquito to be a vector. Though voluminous literature is available on the susceptibility of various anophelines of the world, only a few studies have been carried out in India on the susceptibility of anophelines to human plasmodia. They include studies by Strickland (1933) on An. stephensi, Russell and

All these anophelines developed the infection (though not at all the instances) except An. barbirostris (Russell and Mohan, 1939a) but with varying degrees. Studies have also been carried out susceptibility of An. tessellatus and An. elegans, but only to simian malaria parasites (Choudhury et al., 1963).

Studies showed that there were variations in the susceptibility to malaria parasites between different species of anophelines as well as the same species from different geographical origin. The susceptibility of An. fluviatilis was reported to be 53% to P. falciparum (Mohan, 1955) and 9.4 to 34.4% of An. culicifacies supported the development of P. malariae and P. falciparum respectively (Siddon, 1944; Russell and Mohan, 1939a). The infection rate in An. subpictus to P. falciparum and P. vivax varied from 0 to 33.3% (Russell and Mohan, 1939a; Roy, 1943, Das et al. 1979 and Nanda et al. 1987). The infection rate was 11.7% in case of An. varuna (Russell and Mohan, 1939a).

The susceptibility of Indian anophelines such as An. culicifacies, An. vagus, An. annularis, An. maculatus, An. kochi (Sandosham, 1965), An. culicifacies (Collins et al., 1986), An. jeyporiensis. (Xu, 1986), An. tessellatus (Gamege – Mandis et al., 1993), and An. philippinensis, An. dirus & An. maculatus (Klein et al., 1991c) was studied outside India.
The findings on the susceptibility of *An. subpictus* were contradictory. For example, Das *et al.* (1979) observed that *An. subpictus* failed to develop the plasmodial parasites, while development of parasites was observed by Russell and Mohan (1939a), Roy (1943) and Nanda *et al.* (1987). This might be due to the existence of more than one strain of *An. subpictus*.

No study was carried out on susceptibility of anophelines to *P. malariae* after Siddon's work on *An. culicifacies* (Siddon, 1944), because of rarity of the parasite species (Wernsdorfer and McGregor, 1988).

The varying degree of susceptibility of anophelines is reflected from their natural infections also. In India, *An. fluviatilis* has been ranked first when the vector species are graded in terms of their efficiency in malaria transmission. When the vector responsible for actual number of malaria cases is considered, *An. fluviatilis* occupies second place next to *An. culicifacies* (Rao, 1984). These two species are, therefore, considered as important vectors in India. *An. subpictus* and *An. varuna* are considered as vectors of local importance (Panicker *et al.* 1981; Rao, 1984). *An. tessellatus* is believed to involve in malaria transmission on epidemiological grounds (Rao, 1984). Natural infections were found also in *An. jeyporiensis* and *An. pallidus* but they have been considered as suspected vectors or vectors of no importance because of low infection rates in nature (Rao, 1984). However, their susceptibility status is not known.

### 2.2. Factors influencing the infectivity of gametocytes
Attempts to define the factors that determine infectivity of gametocytes to mosquitoes have been amongst the most elusive endeavors in malaria research.

2.2.1. Gametocyte density

Infection in mosquito vectors with plasmodial gametocytes is regulated by many interdependent factors of parasite, the vertebrate host and the mosquito vector (Boyd, 1949, Dearsly et al., 1990).

Gametocytes with rising numbers produced increasing number of oocysts of P. vivax and P. falciparum (Jeffery, 1952; Jeffery and Eyles, 1955). A linear positive correlation was observed between the number of infective gametocytes and the resulting intensity of the oocyst infection in the mosquito in the laboratory infections with P. gallinaceum (Eyles 1951, 1952 a. b & c and Carter and Gwadz, 1980). A direct correlation was observed between the density of gametocytes of P. falciparum in the blood of a donor and the percentage of mosquitoes infected (Barber et al., 1931, Strickland et al.1933, Russell and Mohan 1939a, 1939b, 1940 & 1941, Knowles and Basu, 1943, Robertson, 1945, Bray and Burges, 1964, Bray et al., 1976 and Graves, 1980).

On the contrary, some studies showed that there was little relation between gametocyte density of P. falciparum, P. vivax and P. gallinaceum and mosquito infection or the number of oocysts they developed (Huff 1927; Kligler and Mer, 1937; Cantrell & Jordan 1946; Young et al.1948; Eyles et al. 1948; Muirhead-Thomson, 1954; Kasap et al., 1987; Graves et al., 1988a; and Sattabongkot et al., 1991).
The question of total leucocyte count in the donor and its correlation with incidence of infection in mosquitoes is also a controversial issue. While Thomson (1914) showed a direct correlation between these two parameters, Green (1929) showed that two were unrelated.

Antibodies to gametes, which act on the parasites after exsheathment in the mosquito gut, are produced in infected human (Graves et al., 1988b. Mendis et al., 1987) but their precise effect on infectivity is unclear since both suppression and enhancement having been reported (Peiris et al., 1988).

2.2.2. Sex ratio of gametocytes

Boyd et al. (1935) reported the effect of sex ratio on the infectivity of *P. falciparum* but not of *P. vivax*. Wernsdorfer and McGregor, (1988) reported that the sex ratio of gametocytes may be a factor in determining minor variability of infectivity but is unlikely to account for major effects in this regard.

2.2.3. Asexual parasitaemia

Studies on *P. gallinaceum* (Centrell and Jordan, 1946; Eyles, 1951), *P. knowlesi* (Carter & Gwadz, 1980) and *P. falciparum* (Rutledge et al., 1969) showed that there is an inverse relationship between asexual parasitaemia and infectivity at any given density of gametocytes. There was a sudden loss of infectivity to mosquitoes when parasitaemia peaked in a *P. cynomolgi* (Hawking et al., 1966) and *P. inui* infection (Dei-Cas et al., 1980).
Effect of asexual parasitaemia on gametocyte infectivity was thought to be due to toxification of the blood produced by the high metabolic activity of the parasites (Wernsdorfer & McGregor, 1988). Rutledge et al. (1969) showed that the presence of moderate number of asexual parasites of *P. falciparum* was associated with increased infectivity to mosquitoes. Whether this relationship is casual or accidental remains a matter of speculation.

2.2.4. Parasite and mosquito strain

Within a *Plasmodium* species, strains of different geographical origin were shown to vary greatly in their infectivity to a particular species of mosquito (Boyd et al., 1938: Boyd & Jobbin, 1940; Young et al., 1946; Eyles & Young, 1950; Jeffery et al., 1950; Bibikova, 1975; Warren & Collins, 1981). It has been believed that apart from the evolved virulence by the parasite, the mosquito species influences the infectivity of the parasite and further provocation of parasites in mosquito body.

The colonised *An. quadrimaculatus* and *An. punctipennis* were equally susceptible to two strains of *P. vivax* but *An. punctipennis* showed variable susceptibility to strains of *P. falciparum* ranging from high susceptibility to complete refractoriness (Boyd & Kitchen, 1936). The colonised *An. albimanus* from Central America, is a highly selective vector and generally susceptible to autochthonous *P. falciparum* and *P. vivax* and is almost completely refractory to either species of parasite originating in continents outside the Americas (Young et al., 1945, 1946; Warren & Collins, 1981). *An. atroparvus* and other European anophelines of the *An. maculipennis* complex are generally refractory to *P. falciparum* of non-European origin such as tropical Africa and Indian subcontinent (James et al., 1932; Shute, 1940; Ramsdale and Coluzzi, 1975; Daskova & Rasnicyn, 1982).
Of 15 strains of *P. vivax* only one from Indonesia was more infectious to *An. culicifacies* than to *An. freeborni*. In general, *An. culicifacies* was more susceptible to *P. vivax* strains from Asia and New Guinea than to those from the new world (Collins *et al.*, 1986).

Some vectors of North America, *An. freeborni* and *An. quadrimaculatus* and the south-east Asian mosquito *An. maculatus* are reported to be infected with *P. vivax* and *P. falciparum* from most major malarious regions including Africa, South-East Asia and Central America (Boyd, *et al.*, 1938; Boyd & Jobbins, 1940; Young *et al.*, 1946; Eyles & Young 1950; Jeffery *et al.*, 1950; Warren & Collins, 1981).

*An. atroparvus*, previously a vector of human malaria in Europe is widely susceptible to *P. vivax* of non-European origin including parasites from south-east Asia, New Guinea, South America, the Indian sub-continent and Arabia (Daskova & Rasnicyn, 1982, Warren & Collins, 1981). Likewise the southern European mosquitoes *An. sacharovi* and *An. maseave* were found to be susceptible to certain *P. falciparum* infections of African origin (Daskova & Rasnicyn, 1982).

*An. sinensis* from Shanghai and Guangxi were experimentally infected with Hainan and Guangxi strains of *P. vivax* (Xu and Ye, 1987). It was found that both of these anopheline mosquitoes had a very low susceptibility to the Guangxi parasite strain, the gland infection rates being 0 and 12.3% respectively. However, they showed distinctly higher susceptibility to the Hainan strain of the parasite, the respective gland infection rates being 36.4% and 43.6%. In *An. minimus*, which served as control, the gland infection rate was 43.2% with Guangxi parasite
strain and 100% with Hainan strain. It was also shown that *An. sinensis* from Wuhan had the same low susceptibility as *An. sinensis* from Guangxi to a Guangxi strain of *P. vivax*, showing that in China, two distinct geographical strains of *P. vivax* with varied infectivity to *An. sinensis* exist (Xu & Ye, 1987).

In a recent study, Collins *et al.* (1993) opined that the ZAN strain of *An. gambiae s.s.* from Zanzibar was more susceptible to infection with the strain of *P. malariae* from Uganda than the G-3 strain of *An. gambiae s.s.* from The Gambia.

Thus, the infectivity of different parasites is entirely dependent upon the species of the mosquito involved and is largely related to the geographic origin of parasite and vector (Wernsdorfer and McGregor, 1988).

### 2.2.5. Human age

The nature of infectious carrier of malaria in an endemic situation is an important consideration in the application of malaria control methods, which are ultimately aimed at reducing transmission be they vaccines, drugs or vector control methods. Nevertheless, few comprehensive studies have been carried out on this aspect.

Studies conducted by Gamage Mendis *et al.* (1991) revealed that infectivity of gametocytes of carriers of the youngest (0 to 5 years) and the oldest (>50 years) age groups appeared to be the lowest. Patients of 6-25 years age group constitute bulk number of carriers in the population, followed by 26-50 years age group. This could be due to the effect of transmission blocking or enhancing antibodies inducing factors. The host immunity interferes
in the process of vector infection and lead to major differences in the nature of the reservoir of infection.

2.2.6. Age of the mosquitoes

The only report by Russell et al. (1963) suggests that younger mosquitoes are more likely to be infected than the older ones.

2.2.7. Ambient Temperature

The incubation period of the parasite in vector i.e. extrinsic/sporogony cycle is determined by parasite species and ambient temperature. At a given temperature, the duration of sporogony was the longest for P. malariae, followed by P. ovale, P. falciparum and P. vivax (Coatney et al., 1971. Shute and Maryon, 1952). The parasite develops in the vector only at certain range of temperature. The minimum ambient temperature, below which the parasite does not develop in the vector, is 15 °C for P. vivax and 19 °C for P. falciparum (MacDonald 1957). It was also shown that above a critical minimum temperature, the incubation period decreases with the increase in temperature. Detinova (1962) however observed the minimum temperature for the development of P. vivax was 14.5 °C. For other malaria parasites it was 16 °C. According to Coatney et al. (1971) it is 15 °C for P. vivax and P. malariae. Rutledge et al. (1969) found that exogenous development of P. falciparum does not occur below 21 °C or above 32 °C, and development of P. vivax does not occur below 16 °C or above 32 °C. Yang et al. (1988) found that the development period of P. vivax in mosquitoes was 9 days at a temperature of 26±1°C. Kasap (1990) recorded complete sporogony of P. vivax in An.
superpictus in 10-14 days with an average of 11.7 days and in An. sacharovi within 8-12 days with an average of 9.8 days.

Studies on the anophelines of erstwhile Koraput district of Orissa

In all the experimental studies in India, colonized mosquitoes were used for the experiments, except by Nanda et al. (1987), who had used F1 generation of An. subpictus s. 1. The limitation in using the colonized mosquitoes for determining susceptibility and trying to extrapolate the information to the wild population is that the colonized mosquitoes would have lost the local genotype. Therefore, susceptibility of vector species with F1 generation and with local strains of parasites would be more relevant in determining their role in transmission and also vector-parasite relationship.

In erstwhile Koraput district, a total of 25 anopheline species has been recorded, of which An. fluviatilis, An. culicifacies, An. subpictus, An. varuna, An. jeyporiensis, An. tessellatus, An. splendidus, An. pallidus and An. theobaldi are abundant (Gunasekaran et al., 1989). Among these, An. fluviatilis and An. culicifacies have been incriminated malaria vectors in the district. In other anophelines, no natural infection was seen (Gunasekaran et al., 1989). Changes in the vectorial status of some anophelines have been documented following the DDT spray program. An. varuna, which was considered as one of the vectors in the pre-DDT era, now appears not to be important in transmission (Gunasekaran et al., 1989). In contrast, An. culicifacies and An. annularis, which were not considered earlier as vectors of malaria in this area, are now incriminated as secondary vectors (Gunasekaran et al., 1989). The vector potential of An. jeyporiensis in malaria transmission remains uncertain. Marked
differences have been reported in the natural infection rates and vectorial capacity of An. fluviatilis population from the two zones in the district.

It is likely that the variations observed in the natural infection between the anopheline species could be attributed to the variations in the susceptibility to the malaria parasites. Absence of natural infections in some of the anopheline species may partly be due to either low susceptibility or refractoriness to the parasites. It is also likely that the variations could be due to the specificity in susceptibility of vector species to the local strain of parasites.

Studies on susceptibility of the known vectors as well as other abundant anophelines to human plasmodia parasites in this area may explain their relative importance in malaria transmission in relation to space and time.