FACTORS AFFECTING MALARIA DISEASE TRANSMISSION AND INCIDENCE: A SPECIAL FOCUS ON VISAKHAPATNAM DISTRICT

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ABSTRACT

Malaria is a vector borne infectious disease wide spread in tropical and subtropical areas. Malaria situation in Visakhapatnam since 1961 is under closed surveillance of National Malaria Programmes. Malarial incidence reduced dramatically with the help of National Antimalarial Programmes, till the resurgence in 1970’s. Recent outbreaks in 1999 with the gradual increase of malarial cases till date in Visakhapatnam demands a case study on factors affecting malaria disease transmission and incidence with special focus on Visakhapatnam district. Review provides new insights about the possible factors contributing to malarial transmission and incidence.

INTRODUCTION

Malaria is severe public health problem in developing countries, which is a complex and fatal disease caused by four species of Plasmodium parasites and transmitted by different number of vectors. Half of the world’s population i.e., 3.3 billion people live in malaria transmission areas of 106 countries and territories at risk. An estimated 216 million positive cases and 655,000 deaths were reported in year 2010 due to malaria. According to WHO report 86% of the malarial deaths were of children (Ahmad et al., 2013). Of this African region, South East Asian region, Eastern Mediterranean region reported 91%, 6%, 3% malaria deaths respectively. Kumar et al. (2007) reported that India alone contributes nearly 77% of the malaria cases in South East region. Visakhapatnam, one of the major districts of Andhra Pradesh state contributes up to 2% of the annual malaria incidence throughout the country with an annual parasite index (API) of 8.46, 8.35 during 1991-95, 1996-2000 respectively.

Malaria Disease Transmission and Incidence

A female Anopheles mosquito while feeding human injects sporozoites of malarial parasites into the bloodstream. The sporozoites travel to the liver and invade liver cells. Sporozoites remain dormant or grow, divide, and produce haploid forms, called merozoites over a period of 15-16 days. The merozoites exit the liver cells and re-enter the bloodstream, beginning a cycle of invasion of red blood cells. Parasite-infected cells in the host bloodstream, lead to ill health and complications of malaria. Some of the merozoite-infected blood cells leave the cycle of asexual multiplication and develop into sexual forms of the parasite, called male and female gametocytes. When a mosquito bites an infected human, it ingests the gametocytes and releases the gametocytes in the mosquito gut, which develop further into mature sex cells called gametes. Male and female gametes fuse to form diploid zygotes, which develop further into ookinetes and form oocysts.

Growth and division of each oocyst produces thousands of active haploid forms called sporozoites in 8-15 days. Upon release of sporozoites they travel and invade the mosquito salivary glands and the cycle of human infection re-starts when the mosquito takes a blood meal, injecting the sporozoites from its salivary glands into the human bloodstream.

Factors Affecting Malaria Disease Transmission and Incidence

Transmission of malaria depends on the factors affecting the disease and varies from place to place. There are areas where the transmission and incidence of disease is high, low and in some areas it is very brief that it lasts for several months or throughout the year. Different climatic and non-climatic factors favor the transmission of the disease. Temperature, rainfall and relative humidity are the climatic variables that influence parasites life cycle in vector as well as in parasites (Gubler et al., 2001; Koenraadt et al., 2004). Non-climatic factors include parasites, vectors, human host factors, population movement or migration, urbanization and interruption of control and preventive measures.

Climatic Factors

Climate change represents a potential environmental factor affecting disease emergence. Shift in the geographic ranges of hosts and vector, effect reproduction, development, and mortality rates on hosts, vectors, and pathogens. Effects of the increased climate variability, floods and droughts all have the potential to affect disease incidence and emergence either positively or negatively. Divya et al., (2013) explained the associations between total, average rainfall and malaria outbreaks. Mosquitoes prefer water bodies and right amount of rainfall is most important factor for them to breed. So, changes in rainfall drive malaria transmission to a higher state (Gao et al., 2012). Blanford et al., (2013) explained temperature as an important determinant of...
malaria transmission. Maximum and minimum temperatures affect the life cycle of malaria parasite. The maximum and minimum temperatures for parasite development are 40°C and 18°C. Below 18°C, the life cycle of *P. falciparum* in the mosquito body is limited. The minimum temperatures of *P. vivax* are between 14–19°C, surviving at lower temperatures than *P. falciparum*. Life cycle of the parasites in vectors can be shorter or longer depending on temperature. A minimum of 10 to 19 days is required for the parasite to complete its life cycle in the gut of mosquito. Sometimes life cycle decreases to less than 10 days as the temperature increases from 21°C to 27°C, with 27°C being the optimum. Malaria transmission in areas colder than 18°C can occur because the *Anopheles* often live in houses, which tend to be warmer than the outside temperature. Mosquito’s survival is greatly influenced by relative humidity as they survive better and become active under conditions of high humidity greater than 60%, if it is below 60% the life cycle of mosquito is short or no malaria transmission. Therefore, rainfall, temperature and relative humidity are the major climatic factors that guide malaria transmission by showing their effect on *Anopheles* mosquitoes.

Statistical methods like correlation (Kim and Jang, 2010), time series analysis (Tian et al., 2008), regression methods (Robert, 2012) were used to understand association between climate and malaria disease and also the effect of climate on malaria disease incidence and transmission. Most of the studies used either individualistic or combined effects of all the three climatic factors on malaria incidence. Studies on climatic variability and its influence on malaria disease in Mahaboobnagar district, Andhra Pradesh, India demonstrated that monthly temperature, rainfall, humidity and mosquito populations (*Anopheles calificacius, A. fluviatalis, A. subpictus* and *A. stephensi*) showed positive correlation with monthly malaria disease incidence (Srinivasulu et al., 2013). Correlation analysis between malaria cases and various meteorological variables (total rainfall, mean of maximum and minimum, and relative humidity) showed positive correlation with monthly incidence of malaria. Mathematical models were developed nearly a century ago and are well established (Macdonald, 1957). A validated spatiotemporal modeling of malaria transmission, three climatic scenarios reported (Mabaso et al., 2006), the impact of climate change on malaria disease incidence and transmission (Parham and Michael, 2010). Development of valid and realistic models that capture climate change on malaria disease and vector populations remains an important research area and a crucial component towards improving the understanding on malaria transmission across a range of environmental changes. Reliability of such models is estimated by forecasting methods and by comparing the past data with the present data and predicting the future risks of the disease incidence rates.

**Non-Climatic factors**

Current scenario on malaria is clearly associated with the social and demographic changes of the past 50 years. Factors that don’t come under the category climate are non-climatic factors. Social factors like urbanization, globalization, population movement, deforestation, interruption to control measures; and biotic factors like human host factors, parasites, vectors are the non-climatic factors that have they role in affecting disease incidence and severity.

**Urbanization**

Rapid urbanization in the world’s population has undergone unprecedented growth, it is estimated that by 2050 the people living in urban areas will increase up to 67% (Qi et al., 2012). Urbanization is associated with greater decline in malaria transmission (Tatem et al., 2013), but the presence of bushes, stagnant water, rainfall, low altitude and high temperatures favor the breeding of malaria vectors as well as parasite development within them (Kimbi et al., 2013), thereby increasing malaria risk.

**Population Movement**

Population movement has contributed to the spread of malaria (Prothero, 1977). Malaria risk may increase in certain regions due to population movement by labor related to agriculture, mining, conflict and refugees, airport malaria, imported malaria (Marten’s and Hall, 2000).

**Deforestation**

Forests have a density of mosquitos; deforestation generally reduces the density of mosquitos at the site of deforestation. Mosquitos rarely travel more than a few kilometers and therefore mosquitos reach to the nearest residential area thereby increasing in the availability of hosts to hosts. Thus, an increase in the entomological inoculation rate to hosts is achieved, subsequently increasing the disease transmission and incidence when there is deforestation.

**Human Host Factors**

Human hosts factors like immunity, age, pregnancy, phenotypes, surface of the erythrocyte cells, ethnic differences, structural variation of globin genes, regulatory variations in globin genes, oxidative stress, antibody response, proinflammatory response and other serum factors provide resistance or susceptibility to malaria infection (Kwiatkowski, 2005) affecting the pattern of malaria transmission and severity of the disease. An immune person has a better chance to eliminate the disease rather than the non-immune ones. Children’s less than five years of age and pregnant women are at high risk because of theirs less immunity.

**Interruption to control and preventive measures**

Several preventive and control methods were used worldwide to eliminate malaria. These include immediate and proper medications to control parasites in humans (chemoprophylaxis), prevention of mosquito bites to humans by mosquito repellents, insecticide treated nets, bednets, indoor residual spraying to control mosquitos, destroying the breeding habitats in water bodies with insecticides and anti-larval operations to control mosquitos. Sustained and long term implementation of preventive and control measures are necessary to significantly reduce or eliminate the problem from a country or in a specific region. If the control measures are stopped or being interrupted malaria can revert back and cause infection to more number of people. Genus *Plasmodium* includes 120 species or more each restricted to a limited number of hosts. Malaria in humans is caused by four main species - *P. falciparum, P. vivax, P. ovale* and *P. malariae*, of which *P. falciparum* and *P. vivax* are predominant in India. Early Diagnosis and Prompt Treatment (EDPT) a part of NVBDCP is not only a curative programme, but also a means to curtail the transmission process. As part of EDPT, the blood samples of patients are smeared on a glass slide and analyzed for presence of parasites.
Drugs like Artemether, Artesunate, Bulaquine, Chloroquine, Mefloquine, Mepacrine, Quinine and related agents, Amodiaquine, Pyrimethamine, Proguanil, Sulfonamides, Mefloquine, Atovaquone, Primaquine, Artemisinin and derivatives, Halofantrine, Doxycycline, Clindamycin are used for treatment of malarial parasite. Immediate antimalarial therapy is followed up for 7 days in case of *P. falciparum* and 28 days in case of *P. vivax*. In addition to drugs a total of 52 vaccines have been developed and some vaccine candidates are being identified and some of them are used against *Plasmodium* species for the following stages of parasite - multistage (Tine et al., 1998, Rafi-Janajreh et al., 2002), pre-erythrocyte (Dolo et al., 1999, Bottius et al., 1996), erythrocytic (Chen 2007, Peek et al., 2006,), asexual blood stage (Graves et al., 1998), sexual stage (Malkin et al., 2005). Drug resistance in parasites is an important factor which interrupts control measures. *Plasmodium* species causing malaria in humans have developed drug resistance to available drugs. Resistance to chloroquine was observed in almost all the areas affected with malaria (Bloland, 2001). Chloroquine resistance was first identified in 1973 in Assam (Sehgal et al., 1973, wide spread (Vathsala et al., 2004) and observed in *P. falciparum* in India and *P. vivax*. But chloroquine remains effective against *P. vivax* in India (Nandy et al., 2003; Valecha et al., 2006).

Similarly high levels of sulfadoxine and pyrimethamine resistance were observed in *P. vivax* in India (Ahmed et al., 2006; Ganguly et al., 2014) Resistance to artesunate combination therapy was yet reported in India. Emergence of drug resistance suggests the need for identifying novel drug targets and drugs for different stages of *Plasmodium* species by using various approaches. *In silico* analysis of genomes, proteomes, and metabolic pathways would provide a source or a pool of new drug targets. A comparative analysis of genomes between host and pathogen, virulent and avirulent strains, set of strains, set of species identify unique genes for the organism. A comparative proteome analysis between host and pathogen would provide information about important unique molecules or enzymes for organism. Metabolic pathway analysis, chokepoints detection and flux balance analysis of metabolomes provides information on metabolically important molecules. Some in vivo and invitro strategies like haploinsufficiency profiling, chemogenomics, chemical proteomics, signature tag mutagenesis, expression profiling and gene knockout technologies are the wet lab techniques that can be used to identify potential drug targets for *Plasmodium* species. Later these drug targets can be validation either by growth bioassays and gene knockout methodologies.

**Figure 1** Map showing the total mandals in the Visakhapatnam district and surrounding border districts to the north Vizainagarm, Srikakulam, east Bay of Bengal, west Orissa state and south Khammam district.

**Figure 2** Yearly data of malarial cases reported by District Malarial Office in district of Visakhapatnam.
These drug targets can be used to analyze the target structures for possible binding/active sites, generate lead candidate molecules, check for their drug likeness, dock these molecules with the target, rank them according to their binding affinities, further optimize the molecules to improve binding characteristics and identify a new drug candidate for *Plasmodium* species. Not all the anophelines mosquitoes can carry the malarial parasites; only female anophelines mosquitoes can transmit malaria. There are about 3,500 mosquito species and those that transmit malaria all belong to a sub-set called the *Anopheles*. Approximately 40 *Anopheles* species were able to transmit malaria and are well enough to cause significant human illness and death. *Anopheles culicifacies*, *A. fluviatilis*, *A. minimus*, *A. Sundaicus* and *A. Stephensi* are dominant malaria vectors in India (Dev and Sharma, 2013). Successful eradication or control of malaria in different places of the world was achieved by controlling the mosquito vector population with different chemical insecticides (Harrison, 1979).

Two types of methods were generally used for vector control first one is indoor residual spraying (IRS) and second option is long lasting insecticide treated nets (LN’s) for controlling malaria transmission (Enayati et al., 2009). In India pyrethrum (Persian insect powder), mercuric chloride, parvis green, phenols, cresols, napthelene, Bordeaux mixture, rosin-fish oil soap, calcium arsenate and nicotine sulphate were used as insecticides in 18th and 19th century (ICMR Bulletin, 2002). Similar to drug resistance in parasites, insecticide resistance in vectors is also one of the major problem for spread of malaria in endemic areas. *A. culicifacies* has developed a wide spread resistance to DDT (organochlorine) due to continuous usage in indoor residual spraying (Sharma et al., 1986, Sharma et al., 1999).

A Special Focus on Visakhapatnam District

Visakhapatnam district stands in 44th place in the country and 5th in Andhra Pradesh state in terms of populations and a geographical area of 11.24 lakhs hectares with long sea coast line (Figure 1). Visakhapatnam the north coastal district of Andhra Pradesh is located between 17° 15’ and 18° 32’ North latitude and 18° 54’ and 83° 30’ east longitude. It is bounded in the north partly by Orissa and Vizianagaram district, in the south by East Godavari district, in the west by Orissa and in the east by the Bay of Bengal. According to the 2011 India census, population of Visakhapatnam is 37, 89, 820 with an area covering of 11,161 square kilometres. Visakhapatnam is the first district receiving high annual malaria incidence in the state with 43 mandals and 86 primary health centres (Figure 1). The coastal regions are pleasantly humid and comfortable, further inland the air gets warmer while in the hill areas it is noticeably cooler on account of elevation and vegetation with little variation in temperature through the year. May is the hottest month with average temperatures around 32°C (90°F), while January is the coolest month with average temperatures near 23°C (73°F). The humidity remains high throughout the year. The total annual rainfall is around 945mm (38inches), the bulk of which is received during the south-west monsoon. October is the wettest month with around 204mm (8 inches) of rainfall.

According to the available data on malarial disease incidence from the year 1984 to 2009, highest number of cases were reported in 1999 (i.e.41,977), followed by a gradual decrease in malaria positive cases till the year 2009 in 2005 (Figure 2) and *Plasmodium falciparum* and *P. vivax* infections were predominant in Visakhapatnam. Narasimha et al., (2010) has studied the municipal wards of Visakhapatnam city tousing liquid quotient method and observed association between rainfall and malarial disease incidence. In this context, a case study in the district of Visakhapatnam to map malarial disease incidence cases; to evaluate relationship between climatic factors, mosquito populations and malarial disease incidence using statistical methods; models and predictions of climatic factors, mosquito populations and malarial disease incidence helps us in identifying malaria transmission patterns to understand Malaria Transmission Mechanism (MTM). Previously National Institute of Malaria Research (NIRM), National Anti-malarial Programme (NAMP), National Malaria Eradication Programme (NMEP), National Malaria Control Programme (NMCP) addressed the rising malarial disease incidence. Currently malarial control programmes fall under the ambit of National Vector Borne Disease Control Programme (NVBDCP), Primary Health Centres (PHC), District Malaria Office (DMO), Indian Council of Medical Research (ICMR) and State Government. These organizations in coordination carry out investigations of malarial epidemics.

Epidemiological investigations in Paderu division of Visakhapatnam district, Andhra Pradesh found chloroquine resistant *Plasmodium falciparum* using the slide positivity rate (SPR). Further, it was found that *A. culicifacies* and *A. fluviatilis* were resistant and susceptible to DDT and Malathion, Deltamethrin respectively (Dhiman et al., 1999). (Srinvasula et al., 2013) identified dominant cerebral malaria cases in tribal populations of Visakhapatnam. (Dantu et al., 2013) further observed that drugs used for malarial treatment induced hemolytic anaemia and variants of enzyme glucose-6-phosphatase dehydrogenase are responsible for hemolysis. The growing problem of malaria in Visakhapatnam demands a case study on efficacy of drugs that are used to control malaria. The same EDPT principle can be applied to the district of Visakhapatnam to understand the efficacy of drug. Studies on climatic variability, vector population, drug efficacy on malarial disease incidence may provide new insights on the disease patterns in Visakhapatnam district.

CONCLUSION

Malaria disease transmission and incidence is affected by a number of factors. Different factors favoring the transmission of the disease are climatic and non-climatic factors. Temperature, rainfall and relative humidity are the climatic variables. Parasites, vectors, human host factors, population movement or migration, deforestation, urbanization and interruption of control and preventive measures are the non-climatic factors. Studies on climatic variability, vector population, drug efficacy on malarial disease incidence in the district of Visakhapatnam may provide new insights on the disease patterns in Visakhapatnam district. Though resistance to artesunate combination therapy was not yet reported in India, emergence of drug resistance to others drugs/current treated drugs in the near future suggests the need for identifying novel drug targets and drugs for different stages of *Plasmodium* species.

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