Vector-borne diseases in central India, with reference to malaria, filaria, dengue and chikungunya

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ABSTRACT

Background: Vector-borne diseases (VBDs) caused by parasites and viruses are a major cause of morbidity and mortality in Madhya Pradesh (MP), central India. These diseases are malaria, lymphatic filariasis, dengue and chikungunya. Epidemiological information is lacking on different VBDs that are commonly prevalent in rural-tribal areas of MP, except on malaria.

Methods: The studies were carried out at the request of Government of Madhya Pradesh, in three locations where many VBDs are endemic. Data on malaria/filaria prevalence were collected by repeatedly undertaking cross-sectional parasitological surveys in the same areas for 3 years. For dengue and chikungunya, suspected cases were referred to the research centre.

Results: Monitoring of results revealed that all the diseases are commonly prevalent in the region, and show year-to-year variation. Malaria slide positivity (the number of malaria parasitaemic cases, divided by the total number of blood smears made) was 18.7% (190/1018), 16.4% (372/2266) and 20.4% (104/509) respectively in the years 2011, 2012 and 2013. There was a strong age pattern in both Plasmodium vivax and P. falciparum. The slide vivax rate was highest among infants, at 5% (odds ratio [OR] = 3.8; 95% confidence interval [CI] = 1.5 to 9.4; P<0.05) and the highest slide falciparum rate was 20% in children aged 1–4 years (OR = 2.0; 95% CI 1.5 to 2.7; P<0.0001). This age-related pattern was not seen in other VBDs. The microfilaria rate was 7.5%, 7.8% and 7.8% in the years 2010, 2012 and 2013, respectively. Overall, microfilaria rates were higher in males (8.7%) as compared to females 6.4% (OR = 1.5; 95% CI = 1.1 to 2.0; P < 0.01). The prevalence of dengue was 48% (dengue viruses 1 and 4 – DENV-1 and DENV-4), 59% (DENV-1) and 34% (DENV-3) respectively, in the years 2011, 2012 and 2013 among referred samples, while for chikungunya very few samples were found to be positive.

Conclusion: Despite recent advances in potential vaccines and new therapeutic schemes, the control of VBDs remains difficult. Therefore, interruption of transmission still relies on vector-control measures. A coordinated, consistent, integrated vector-management approach is needed to control malaria, filaria, dengue and chikungunya.

Key words: Chikungunya, dengue, filaria, malaria, Madhya Pradesh, vector-borne diseases

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INTRODUCTION

Vector-borne diseases (VBDs) caused by parasites and viruses are major causes of morbidity and mortality across the world, especially in tropical and subtropical low- and middle-income countries. Malaria, lymphatic filariasis, dengue and chikungunya are important VBDs, with a major contribution to the overall global disease burden every year.

Malaria is a major public health problem, causing 207 (range 135 to 287) million cases and 0.627 (range 0.473 to 0.789) million deaths throughout the world in 2012. One hundred and four countries and territories are endemic for malaria, and India alone contributes about 50% of the 2 million reported cases in the World Health Organization (WHO) South-East Asia Region. The majority of malaria cases and deaths in India are reported from Chhattisgarh, Jharkhand, Madhya Pradesh, North Eastern States, Orissa and Rajasthan. There are six efficient vectors of malaria, of which three are common in central India, namely Anopheles culicifacies, A. stephensi and A. fluviatilis.

Lymphatic filariasis is endemic in 81 countries in tropical and subtropical regions of Asia, Africa, central and southern America and Pacific Island nations, with more than 120 million people infected and 1.34 billion people at risk of infection. An estimated 25 million have genital disease and 15 million have lymphoedema or elephantiasis caused by Wucheraria bancrofti or Brugia malayi. India alone contributes 40% of global cases of lymphatic filariasis. In India about 600 million people, residing in 250 districts, are at risk. There are about 31 million microfilaria carriers and 23 million chronic clinical cases. Lymphatic filariasis is caused mainly by W. bancrofti (>99%) and transmitted by mosquito – Culex quinquefasciatus.

Dengue fever is a most important re-emerging arboviral disease, causing an estimated 390 million infections every year worldwide, of which nearly 100 million require medical attention, and more than 500 000 require hospitalization. It is estimated that 34% of the global cases are from India and the country is known to be endemic, with all four serotypes (DENV-1, DENV-2, DENV-3 and DENV-4) circulating throughout the year in different parts. Aedes aegypti is regarded as the principal vector for this virus in India.

Chikungunya virus (CHIKV) is a mosquito-transmitted single-stranded RNA alpha virus belonging to the family Togaviridae. There is historical evidence that CHIKV originated in Africa and subsequently spread to Asia. A characteristic feature of CHIKV is that it causes explosive outbreaks, before apparently disappearing for a period of several years to decades. In 2005, the disease re-emerged in the Indian Ocean, after 32 years, and over 1.3 million cases of chikungunya are estimated to have occurred in India. The disease is overshadowed by dengue, which has similar symptoms and is transmitted by the same vector; as a result chikungunya is neglected because the symptoms are milder in comparison to dengue.

This study aims to describe the characteristics of VBDs that are commonly prevalent in central India, to help policy-makers to commence appropriate, evidence-based strategies for curbing these diseases. The results reported fill some knowledge gaps with regard to the burden associated with these VBDs in Madhya Pradesh.

MATERIALS AND METHODS

The study has the approval of the ethics committee of the Regional Medical Research Centre for Tribals (RMRCT), Jabalpur.

Study area

Madhya Pradesh is situated in the centre of India and comprises 50 districts. At the request of the Government of Madhya Pradesh, the studies on malaria, lymphatic filariasis and dengue were carried out in the districts of Anuppur, Panna and Narsinghpur respectively (see Figure 1). State-wide analysis of chikungunya was also carried out. RMRCT, Jabalpur is the WHO collaborative centre for the health of the indigenous population and the National Vector Borne Disease Control Programme (NVBDCP) designated apex referral laboratory for dengue and chikungunya, for Madhya Pradesh and Chhattisgarh.

Anuppur district

Anuppur is located at 23.1°N 81.68°E, with an average elevation of 505 m. The district is about 300 km from RMRCT, Jabalpur, has an area of 3701 km² and one third of the area is under forest. The population of the district is 749 237, of whom 48% are ethnic tribes. The villages are located off road and the terrain is inaccessible. The study area is on the border of the Bilaspur and Korea districts of Chhattisgarh state. Most tribal villages are formed of three to eight scattered hamlets, encircled by perennial streams and their tributaries. These streams supports numerous breeding sites for A. culicifacies and A. fluviatilis, throughout the year. The inhabitants of the villages are of the primitive Baiga tribe and the local economy is mainly forest based. The area is under two rounds of indoor residual spray (IRS) with dichlorodiphenyltrichloroethane (DDT) for vector control. The inhabitants spend most of their time outside their dwellings and sleep outdoor during hot and humid seasons, or in agricultural fields for crop protection. In all, 12 cross-sectional parasitological surveys were carried out for malaria during 2011–2013, covering all seasons i.e. spring (February to March), summer (April to June), monsoon (July to September), post monsoon (October to November) and winter (December to January). Spleen examination was carried out in children aged between 2 and 9 years, with or without fever, using Hackett’s method.
Panna district

Panna is located at 24.27°N 80.17°E, with an average elevation of 410 m. Panna district is highly endemic for filariasis and about 200 km from RMRCT, Jabalpur. Panna has an area of 7135 km², of which 49% is under forest. The population of the district is 1,016,520, of whom about 88% live in rural areas (only 15.4% ethnic tribe) and they are engaged mainly in agricultural activities. From 2004, mass drug administration (MDA) started in the district, and by June 2013 eight rounds were completed. Microfilaria surveys were carried out in randomly selected villages that historically had clinical cases related to filarial disease. Among these, sentinel villages under NVBDCP were also surveyed. A total of three surveys were carried out in the years 2010, 2012 and 2013.

Narsinghpur district

Narsinghpur is located at 22.95°N 79.2°E, with an average elevation of 347 m. The district has an area of 5125.55 km², with a population of 1,091,854 and is about 90 km from RMRCT, Jabalpur. Forest covers 26.6% of the geographical area and the inhabitants of the study area belong to a low socioeconomic group and are employed in agricultural practices. Blood samples from patients with suspected dengue in Narsinghpur during 2011 to 2013 were referred to RMRCT for laboratory testing.

Madhya Pradesh state

Blood samples of patients in Madhya Pradesh state with suspected chikungunya during 2011 to 2013 were referred to RMRCT for laboratory testing.

Sample processing for malaria, filaria, dengue and chikungunya

For malaria, thick and thin blood smears were made from all fever cases and cases with a history of fever in the past 14 days, after obtaining written informed consent. Blood smears were stained with Jaswant Singh and Bhattacharji stain and examined under a microscope as described earlier. Treatment was provided as per national drug policy on malaria, i.e. artesimin-based combination therapy (ACT) + primaquine for *Plasmodium falciparum* and chloroquine + primaquine for *P. vivax*. Pregnant women and infants were not given primaquine. Before undertaking this investigation, data from the district in previous years were obtained from the district malaria officer Anuppur, along with details of the insecticide used for spray and the population covered (see Table 1).

For lymphatic filariasis, blood slides were prepared by conducting night blood surveys between 8 pm and 11 pm, from a randomly selected population; 40 µL of blood was taken from a finger prick and a thick smear was prepared and
stained as described earlier. Treatment to microfilaria carriers was provided by the district medical officer, as per NVBDCP guidelines.

For dengue, the blood samples from suspected patients were collected by the treating physician and referred to the laboratory in the cold chain, with information in a predesigned format. All the samples collected after the fifth day of illness were tested for the presence of DENV-specific immunoglobulin M (IgM), by enzyme-linked immunosorbent assay (ELISA), using a kit developed by the National Institute of Virology (NIV), Pune, India as per the manufacturer’s protocol. The samples collected in the acute phase of illness (in the first 5 days) were tested either for the presence of nonstructural (NS1) protein by using the dengue day 1 diagnostic test (DENGUE DAY1 TEST, J Mitra and Co. Pvt. Ltd. New Delhi, India) and/or by nested reverse transcription polymerase chain reaction (nRT-PCR), with minor modification. The PCR products were sequenced to identify genotypes, using the basic local alignment search tool.

For diagnosis of chikungunya, samples were referred from all over the state. These samples were tested for the presence of CHIKV IgM antibodies, using a kit manufactured by NIV, Pune. The samples collected in the acute phase of illness were subjected to RT-PCR, as described by Naresh et al. (2007). A few, randomly picked, dengue-negative samples were also tested for the presence of CHIKV IgM and the PCR products were sequenced.

Data analysis

The demographic and clinical information of patients was double-key entered into Microsoft Excel 2007. All records were validated and all inconsistencies and differences were resolved before analysis. Statistical analyses were performed using STATA 12 for Windows (StataCorp LP, Texas, United States of America). Categorical data are presented as frequency counts (%) and compared using the χ² or Fisher’s exact statistic as appropriate. Odds ratios (ORs) and 95% confidence intervals (CIs) were also presented for 2 × 2 contingency tables. The significance level was considered alpha = 0.05 and at 95% confidence level.

Study definitions

The slide positivity rate (SPR) was defined as the number of malaria parasitaemic cases, divided by the total number of blood smears made. The slide falciparum rate (SFR) and slide vivax rate (SVR) were defined as the number of falciparum- and vivax-infected cases respectively, divided by the total number of blood smears made. The microfilaria rate was calculated as the number of microfilaria-positive cases out of the total number of blood smears examined.

RESULTS

Malaria slide positivity was 18.7% (190/1018), 16.4% (372/2266) and 20.4% (104/509) respectively in the years 2011, 2012 and 2013. The age-specific and species-specific data on malaria are shown in Table 2. Both P. vivax (16.1%; 107/666) and P. falciparum (82.3%; 548/666) were prevalent in all age groups, with a few cases of mixed infection with P. vivax and P. falciparum (1.2%; 8/666). Only three cases of P. malariae were found. Young children between 1 and 4 years of age showed the highest rate of parasite positivity. A decrease in malaria positivity was recorded in relatively older children in the age groups >4 years to 8 years and >8 years to 14 years. An additional decrease in malaria positivity was seen in older children and adults (>14 years). Further analysis revealed that the SFR was highest in infants (<1 year; OR = 3.8; 95% CI = 1.5 to 9.4) when compared with adults (P < 0.05). However, the SFR was highest in young children >1 year to 4 years (OR = 2.0; 95% CI = 1.5 to 2.7) as compared to adults (P < 0.0001). The gametocyte rate was 20.8%, 21.1%, 11.9%, 10.6% and 4.2% in the age groups <1 year, >1 year to 4 years, >4 years to 8 years, >8 years to 14 years, and >14 years, respectively. In adults, the gametocyte rate was significantly lower than in other age groups (see Table 2).

Analysis of the distribution of malaria cases by species of parasite and season revealed (data not shown) that P. falciparum was the dominant species in all surveys. The SFR was highest (25%) in the post-monsoon season (OR = 3.1; 95% CI = 2.0 to 4.9), followed by winter (24%; OR = 2.9; 95% CI = 2.1 to 4.0), and lowest in monsoon (10 %). Year-wise analysis revealed that SPR and SFR increased from 18.7% and 14.9% in 2011 to 20.4% and 19.1% in 2013, though the difference was not statistically significant. The proportion of P. falciparum increased from 80% in 2011 to 93% in 2013 (OR = 1.3, 95% CI = 1.0 to 1.8). The prevalence of splenomegaly was 35.5% (338/950) in 2012, which increased to 40.6% in 2013 (67/165). The average spleen enlargement was 1.82.

For lymphatic filariasis, 3016 individuals were screened during three surveys carried out in Panna district (see Table 3). The microfilaria rate was 7.5%, 7.6% and 7.8% respectively in the
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years 2010, 2012 and 2013. Both sexes were infected but the overall microfilaria rate was higher in males (8.7%) as compared to females (6.4%). This difference was statistically significant (OR = 1.5; 95% CI = 1.1 to 2.0; \( P < 0.01 \)). Monitoring of drug distribution and compliance revealed that coverage was 43% and the compliance rate was 19%.

For dengue, 31 samples were referred from Narsinghpur district in 2011, of which 48% were positive (DENV-1 and DENV-4). In 2012, a total of 123 samples were referred and, of these, 59% were positive (DENV-1), while in 2013, 141 samples were tested, of which 34% were positive (DENV-3). Further analysis revealed that adults in the age groups 26–45 years had the highest numbers of dengue cases, as compared to other age groups, although this was not statistically significant (see Table 4). It was interesting to note that about 5% of dengue-positive cases were admitted to the tertiary care government hospital at Jabalpur (referral hospital) in 2011 and 2012 when DENV-1 and DENV-4 were detected, while 50% of dengue patients were admitted to tertiary care for treatment when DENV-3 was detected. Analysis further revealed that the DENV-1 (genotype III) in 2011 and 2012 and DENV-3 (genotype III) in 2013 were circulating in the area.

For CHIKV infection, out of 364 tested samples, 20 were found to be positive. Nine samples were found positive by nRT-PCR. The sequencing and phylogenetic analysis revealed that the virus belonged to the East Central South African genotype. In the years 2011 and 2012, all the positive cases reported were from Jabalpur district, whereas in 2013, two chikungunya cases were detected in the samples referred from Mandsaur district of west Madhya Pradesh, while two cases were among travellers returning from the southern part of India.

### DISCUSSION

The morbidity and mortality associated with VBDs pose a growing problem for global public health. Studies such as the current one are crucial for understanding the dynamic nature of malaria, lymphatic filariasis, dengue and chikungunya, in this extremely heterogeneous epidemiological landscape.
The risk of malaria within the country varies dramatically, as several distinct malaria ecotypes exist. Forest malaria is a well-characterized ecotype associated with high transmission of malaria. In this study area, malaria transmission is perennial, with both \( P. vivax \) and \( P. falciparum \) present in all surveys. More than 45% of cases were reported in children aged less than 8 years and 34% cases were reported in children aged between 8 years and 14 years. Only 20% of infections were found in older children and adults. The number of malaria cases and age groups indicated that the risk for the age group under 8 years was two times greater than in older age groups, as recorded earlier. There is evidence that, as transmission intensity increases, the age of peak morbidity decreases. Interestingly, a recent study reported a shift in the mean age of malaria cases after introduction of intervention measures in Orissa (long-lasting insecticidal nets [LLINs] + ACT). In spite of high malaria positivity, the insecticide-treated nets (ITNs)/LLINs are not distributed, nor is the area sprayed with synthetic pyrethroid. Only two rounds of DDT were sprayed, and resistance to this insecticide is common among vectors.

It is worthwhile to mention that tremendous progress has been made in some countries in reducing malaria-related morbidity and many countries are striving for elimination of malaria. Amidst this progress, a major challenge is in forested areas, which are not approachable throughout the year and which are dominated by socioeconomically disadvantaged people of tribal origin. These high-risk populations may carry infection from their workplace to their villages, or may be at higher risk of infection because of behavioural factors. Moreover, a large proportion of people are sleeping in the forest unprotected, particularly during October to December, when falciparum transmission is highest. Although the feeding behaviour of vectors was not studied in this area, earlier studies have revealed that vectors bite both indoors and outdoors. Malaria control remains difficult if foci are located in forested areas, owing to the complexities of human behaviour and of scaling up malaria-control measures. Several independent studies have reported that the incidence of malaria in the country is grossly underestimated. This is mainly due to lack of proper surveillance, particularly in remote areas.

Lymphatic filariasis is in the elimination phase in several countries, including India. However, the rates of microfilaria recorded in this study showed that this area is still highly endemic for filariasis after the eighth round of mass drug administration. Records revealed that four rounds of mass drug administration were carried out with diethylcarbamazine (DEC) alone, with a further four rounds with DEC + albendazole. Available literature reveals that five or more rounds of a good compliance rate of mass drug administration reduce the microfilaria rate to below 1%, where it is expected that transmission ceases. Overall, the microfilaria rate of Panna district is ≤1%, according to the state VBD control programme. However, foci and hot spots for filaria are still present, from where it can spread to areas that are currently free of filaria transmission. To stop transmission, the mass drug administration should be with DEC + albendazole, with more than 60% compliance. The present study shows the need to improve the delivery system of drugs and to strengthen information, education and communication (IEC) and behaviour-change communication (BCC) for better drug compliance.

Moreover, Panna district is also endemic for malaria and, recently, 16 samples were referred for dengue, of which 56% were positive for DENV-3.

Dengue is the fastest re-emerging arboviral infection transmitted by \( Aedes \) mosquitoes. The four antigenically distinct dengue viruses (DENV-1 to -4) cause a wide range of signs and symptoms, with marked differences in clinical severity, ranging from asymptomatic infections to undifferentiated fever, dengue fever, dengue hemorrhagic fever and dengue shock syndrome. The four serotypes of DENV showed wide variation over time in epidemiology and clinical presentation. Moreover, besides differences in serotypes, other factors such as sequence variation and primary and secondary infections are known to influence the clinical manifestations. The incidence of dengue is increasing worldwide, in terms of both the number of reported cases and the number of countries where the disease is emerging or re-emerging. There are many reasons for the increase in reported cases: the spread of disease is enhanced by frequent international travel, thereby increasing the movement and exposure of viraemic people; increasing urbanization, which favors man–mosquito contact; and, above all, ineffective vector-control measures. It is worth mentioning here that Narsinghpur is not only endemic for dengue; evidence of lymphatic filariasis was also found in this district, which was non-endemic earlier.

Historically, CHIKV too has been documented to be circulating in central India for over half century and the virus was isolated from both human and mosquitoes from Nagpur city in 1965. The present study, conducted over the last 3 years, confirms the circulation of CHIKV in the central part of India. Although this study has the limitation of small sample size and a low number of referred samples, it underlines that the ECSA genotype of CHIKV is in circulation in Madhya Pradesh; it is important to monitor the virus activity, as CHIKV is known to spread very fast, especially in immunologically naive populations, and can cause long-lasting arthritis resulting in clinical complications.

To conclude, malaria, lymphatic filariasis, dengue and chikungunya are all transmitted by mosquitoes and, in areas where more than one disease is endemic, these diseases can be potentially controlled by the same interventions or strategies. Despite recent advances for potential vaccines and new therapeutic options, the control of VBDs remains difficult. Therefore, interruption of transmission still relies on vector-control measures. This suggests the need for a better coordinated, multi-disease strategy for vector control, wherever these diseases are endemic. Vector control through the use of physical, biological and chemical methods is an important component of prevention of VBDs. However, these methods face several obstacles, in particular the development of insecticide resistance in the vectors and the drastic reduction of chemicals available for public health. WHO encourages adoption of the integrated vector-management strategy, which is a rational decision-making process for optimal use of available resources. One of the key features of integrated vector
management is capacity-building at the operational level, to plan, implement, monitor and evaluate vector control and its epidemiological and entomological impact. To improve the coverage and utilization of interventions, a regularly updated, interactive, comprehensive and sustained national advocacy (IEC/BCC) campaign is required.

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