SPATIAL AND TEMPORAL PATTERNS OF IMPORTED MALARIA CASES AND LOCAL TRANSMISSION IN TRINIDAD

DAVE D. CHADEE AND URIEL KITRON

Insect Vector Control Division, Ministry of Health, St. Joseph, Trinidad, West Indies; College of Veterinary Medicine, University of Illinois, Urbana, Illinois

Abstract. Over a 30-year period (1968–1997) 213 malaria cases in Trinidad were investigated by the Trinidad and Tobago Ministry of Health. Using a global positioning system and a geographic information system, we mapped the precise location of all reported malaria cases, and associated them with breeding habitats of anopheline vectors. The majority of the cases (138, 63%) were individual imported cases around the big port cities. Plasmodium falciparum was the most common parasite, and Africa the most common source of imported cases. Two clusters of cases occurred: an introduced P. vivax outbreak associated with Anopheles aquasalis in 1990–1991, and an autochthonous focus of P. malariae associated with An. bellator and An. homunculus in 1994–1995. Application of a space-time statistic showed a significant clustering of P. malariae cases, and, to a lesser extent of P. vivax cases, but not of P. falciparum cases. Based on potential for occurrence of local transmission, we are developing risk maps to determine surveillance priorities, outbreak potential, and necessary degree and spatial range of control activities following case detections.

Within the Americas malaria is a major cause of disease and death, with 21 countries reporting more than 1 million cases per year, and 280 million people at risk.1 Within the Caribbean Basin only Hispaniola is endemic for malaria, with the rest of the islands having successfully eradicated malaria during the global DDT campaign of the 1950s and early 1960s.2

Trinidad and Tobago was declared free of malaria in 1965,3 but by 1986, 114 imported cases and 15 relapse cases were detected and successfully treated.4,5 Since then, sea and air transportation have facilitated long-distance importation of malaria pathogens to potentially receptive sites where these pathogens may become established and be transmitted to susceptible populations. For example in 1991, 25 years after the successful eradication of malaria, an outbreak of Plasmodium vivax occurred in the small town of Icacos, Trinidad, located in the southwest corner of the island, 19 km from Venezuela. The index case was an adult male infected in Pernaneles, Venezuela during November 1990 who never sought treatment. This resulted in local transmission to 9 individuals in an area adjacent to the Icacos Swamp, where the adult Anopheles aquasalis Curry density was 178 per human-hr during peak biting times.5,6

Local transmission following the introduction of malaria by imported cases or recrudescence in native carriers is of concern in many countries following local outbreaks around airports and other sites in Europe and the United States.7

In Trinidad 4 main vectors have been identified: An. aquasalis, the main vector in coastal swamps;8 An. bellator Dyar and Knab, the vector of bromeliad malaria;9,10 An. albitalis Lynch-Arribalzaga, found mainly in rice fields;8 and An. oswaldoi (Peryassu) found in small running streams.6 Thus, with efficient malaria vectors and the continuous importation of malaria cases, the island remains at risk of re-introduction of malaria, with potential severe consequences, including high rates of morbidity and mortality given that much of the population lacks immunity.

Geographic information systems (GIS) and global positioning systems (GPS) allow for the precise locating and mapping of malaria cases. These epidemiologic data can be associated with entomologic and environmental data, some of the latter derived from satellite imagery.11–15 These georeferenced data can be subject to spatial analysis to prioritize surveillance and control strategies.16–20

The purpose of this study was to map and analyze the spatial and temporal distribution of all malaria cases in Trinidad since malaria eradication. In addition, by quantifying the space-time clustering of all cases, occurrence and risk of local transmission according to parasite species could be evaluated. This information is of use to the Trinidad and Tobago vector control program in determining priorities and allocating resources for surveillance and intervention efforts.

MATERIALS AND METHODS

Regular surveillance for imported cases was initiated in 1965 by the Insect Vector Control Division (IVCD), Ministry of Health, Trinidad. From 1965 to 1997, all patients with febrile illness and a history of travel or residence in malarious countries were referred by hospitals and private physicians to the IVCD. In addition, malaria evaluators were stationed at individual health centers to prepare blood smears from individuals with febrile illnesses. Blood smears were also made from each patient referred to the IVCD. All blood smears were examined for malaria parasites.

This was a retrospective study using data routinely collected by the Ministry of Health, some of which were already published (the data were not collected for the purpose of this study). A standard informed consent form was signed by all patients on admission to the hospital. The study was reviewed and approved by the Ethical Review Committee of the Ministry of Health of Trinidad and Tobago.

Following the positive identification of a malaria case a thorough investigation is initiated to classify cases, and to determine whether local transmission had occurred. When the extrinsic incubation period has elapsed, malaria evaluators are deployed to conduct mass blood smear surveys and the health centers, physicians, hospitals, and all health care workers in the vicinity are put on the alert for febrile illnesses. Because malaria was eradicated in 1965, an effective national surveillance program was initiated and maintained from 1965 to 1997 and no drugs for self-treatment...
are readily available. Therefore, it is unlikely that any clinical cases of malaria were missed by the surveillance network. In addition, no cases of malaria have been detected after autopsy.

All malaria cases classified as follows: imported cases were those brought into Trinidad, a malaria free country, due to the tremendous increase of human mobility and particularly to air and sea travel; cryptic cases were isolated cases of malaria ascertained by appropriate epidemiologic investigation but not associated with introduced cases; and introduced cases were cases of malaria acquired by mosquito transmission from an imported case in an area where malaria does not occur regularly.

During 1997 and 1998, location of every case was determined using a GPS (Trimble GeoExplorer; Trimble Navigation, Sunnyvale, CA and Garmin GPS 45; Garmin International, Inc., Olathe, KS). Precise coordinates of all cases were entered into a GIS (ArcView, ESRI, Redlands, CA), and associated with attribute data of Plasmodium species, year, and source (country) of infection. Spatial and temporal distribution maps were produced using ArcView GIS. The georeferenced database was used to calculate spatial distances between malaria cases.

All cases were tabulated according to parasite species, year and origin. Mixed infections were counted twice when considering parasite species, once otherwise. Descriptive statistics were calculated for the distribution of cases according to year, source and parasite species for each variable separately and for associated variables using Microsoft (Redmond, WA) Excel® data analysis capabilities. Chi-square statistics were used to compare changes in distribution of parasite species and origin over time.21

The spatial and temporal distribution of all malaria cases was analyzed with a $k$ nearest neighbor ($k$-NN) statistic for space-time clustering²² using the Stat! Statistical software for the clustering of health events (Biomedware, Ann Arbor, MI). The distributions of cases associated with each of the 3 main parasite species were analyzed separately to detect space-time clusters of cases. Unlike the Knox space-time statistic,²³ which is based on geographic distance, and depends on the selection of critical space-time distance, the $k$-NN statistic is the number of case pairs that are $k$th nearest neighbors when both space and time are considered. The statistic is

$$
\Delta J_k = J_k - J_{k-1} = \sum_{i=1}^{N} \sum_{j=1}^{N} s_{ik} t_{jk}
$$

where $\Delta J_k$ is the number of space-time nearest neighbors added by increasing $k$ by 1, and are independent of one another for different $k$s. The $k$-NN procedure in the Stat! Software provides the $\Delta J_k$ values and significance levels for $k$ ranging from 1 to 10. The null hypothesis is that nearest neighbor relationships in space and time are independent from each other. When $\Delta J_k$ is significant, the interaction at the $k$ space-time scale is consistent with local transmission of malaria.

### RESULTS

Of 213 cases, more than 40% (89) were *P. falciparum*, with 30% (64 cases) and 25% (54 cases) of *P. vivax* and *P. malariae*, respectively. Mixed infections were rare (2 *P. falciparum* with *P. vivax* and 3 *P. vivax* with *P. malariae*), and only 1 case of *P. ovale* was detected. Of the 213 cases, 164 were imported and could be assigned to a country of origin. Of these imported cases, nearly 50% (80 cases) originated in Africa, and around 25% from South America (45) and Asia (39). Forty-nine cases were acquired locally or classified as cryptic. Cases originated from 23 countries, with Nigeria (48 cases), Guyana (34), and India (34) the major contributors (Table 1).

When parasite species of imported cases was associated with continent of origin, the vast majority (63 of 79) of cases from Africa were *falciparum* malaria, the majority (31/42) of cases from Asia were *vivax* malaria, and equal proportions (23/47) of cases of *falciparum* and *vivax* malaria from South Africa...
America were imported. Nearly 70% (63 of 91) of all *Plasmodium falciparum* malaria cases were from Africa, and more than 50% (31 of 58) of *Plasmodium vivax* malaria cases originated in Asia.

The total number of imported cases has been on the increase from 21 in 1968–1977 to 74 in 1988–1997 (Table 2). The proportion of imported malaria cases from Africa has decreased from 71% in 1968–1977 to 37% in 1988–1997 ($\chi^2 = 7.45, P < 0.01$), while the proportion from South America has increased from 10% in 1968–1977 to 45% in 1988–1997 ($\chi^2 = 8.65, P < 0.01$). The proportion of cases from Asia has not changed (19% in 1968–1977 and 18% in 1988–1997; $\chi^2 = 0.03, P > 0.5$).

When all cases (imported, cryptic, and locally acquired) are considered, the number of cases has increased over time nearly 3-fold from 30 in 1968–1977 to 112 in 1988–1997. Although the numbers of cases of malaria associated with each species increased, (Table 2, mixed infections counted twice) the proportion of *Plasmodium falciparum* malaria cases decreased from 47% (14 of 30) to 34% (40 of 116) and the proportion of *Plasmodium malariae* cases decreased from 40% (12 of 30) to 29% (34 of 116) between 1968–1977 and 1988–1997, but these decreases were not significant ($\chi^2 < 1.6, P > 0.2$). Only the proportion of *Plasmodium vivax* malaria increased significantly from 13% (4 of 30) to 36% (42 of 116) ($\chi^2 = 5.78, P < 0.02$).

The spatial and temporal distribution of malaria cases in Trinidad is shown in Figure 1 and 2. Imported malaria cases from all sources are concentrated around the large port cities of Port of Spain and San Fernando on the west coast of the island. When all cases are considered by year, a concentration of recent cases inland is noticed (Figure 1). This is associated with the re-emergence of *Plasmodium malariae* in the mid-1990s. This pattern is even clearer when the distribution of cases by parasite species is plotted (Figure 2). *Plasmodium malariae* cases are concentrated in the center of the country in the Nariva-Mayaro area. The cluster of *Plasmodium vivax* cases in Icacos in the southwest corner tip of Trinidad is also apparent.

The spatial and temporal clustering of malaria cases was analyzed statistically with the $k$ nearest neighbor statistic. Each of the 3 types of malaria cases, *malariae*, *vivax*, and *falciparum* (mixed infections were considered twice and included with each species) was considered separately (Table 3).

The results indicate that *Plasmodium malariae* cases cluster such that the second and 7th nearest neighbors in space are significantly ($\Delta J_2 = 30, P < 0.01$ and $\Delta J_7 = 41, P < 0.02$) nearer to the second and seventh nearest neighbor in time than is expected under the null hypothesis (random assignment of times to locations). Such interaction at a small space-time scale is indeed consistent with a local transmission of cases. For *Plasmodium vivax*, significant clustering in space and time was found only when the first nearest neighbor was considered ($\Delta J_1 = 13, P < 0.02$). This is probably associated with the highly localized outbreak in Icacos, where all cases occurred within 1 km of each other and in the same year, and to a few other clusters of imported cases. *Plasmodium falciparum* cases showed no clustering at any space/time interval ($P > 0.1$ for all $k$s), indicating that all cases were imported and that no local transmission took place.

**DISCUSSION**

The spatial distribution of malaria cases is associated with the source of infection. For *Plasmodium falciparum* and *Plasmodium vivax*, near-
ly all cases are imported, most of them associated with foreigners or returning nationals that were infected outside the country. Thus, nearly all infections associated with these 2 species occurred in the large towns, mostly Port of Spain and its surroundings, and San Fernando. An exception was the 1991 Icacos outbreak of \textit{P. vivax}, but even these 9 locally acquired cases could be directly associated with an imported index case and were highly localized in a small port town. The main vector incriminated during this malaria episode were \textit{An. aquasalis} collected at a density of 178 per human-hr during peak biting times.\textsuperscript{5}

In contrast, \textit{P. malariae} cases occurred mostly in the central part of the island, in the Nariva-Mayaro area. Most of these cases are recrudescent cases or the result of local transmission associated with bromeliad malaria vectors. In this part of the island, the Immortelle tree, \textit{Erythrina micropteryx Poeppl.}, which was imported from Peru to shade the cocoa trees is a favored host for bromeliads, which in turn provide the breeding habitat for \textit{An. bellator} and \textit{An. homunculus}, \textsuperscript{9} and opportunities for effective transmission of \textit{P. malariae} in this rural area. Despite a density of 60 and 30, respectively, per human-hr during peak biting times, none of 3,100 \textit{An. bellator} and \textit{An. homunculus} mosquitoes tested by ELISA were found positive.\textsuperscript{24}

The application of a GIS and a space-time statistic provided visual and quantitative confirmation of the suspected local transmission of \textit{P. malariae} in the interior of Trinidad and the outbreak of \textit{P. vivax} in the southwest corner. The management of malaria surveillance data in a geographic information system will allow for the rapid production of maps and statistical analyses that will identify clusters of cases and assist in directing the necessary resources for control activities.

The results of this study indicate that local transmission is most likely to follow the detection of a \textit{P. malariae} case in areas where \textit{An. bellator} is common. Because the vast majority of \textit{P. vivax} and \textit{P. falciparum} are imported cases in urban areas, individual cases are unlikely to result in further transmission. The exceptions are the few cases that are imported into coastal marshy areas where \textit{An. aquasalis} is common or close to rice fields where the \textit{An. albicaris} is the main vector.

Based on this analysis of all cases detected over a 30-year period, the uniform policy for follow-up surveillance and control of each detected case can be revisited. The cost of such an intense surveillance and control program is high, averaging $10,000.00 U.S. per case. We propose that based on past experience, a differential approach be adopted, which will be based on intensive active surveillance and

\begin{table}[h]
\centering
\begin{tabular}{|c|c|c|c|}
\hline
$K$ & \textit{falciparum} & \textit{vivax} & \textit{malariae} \\
\hline
1 & 6 & 13\textsuperscript{†} & 13 \\
2 & 30 & 25 & 30\textsuperscript{‡} \\
3 & 49 & 43 & 26 \\
4 & 62 & 57 & 23 \\
5 & 67 & 61 & 26 \\
6 & 100 & 68 & 26 \\
7 & 80 & 84 & 41\textsuperscript{†} \\
8 & 117 & 76 & 30 \\
9 & 97 & 70 & 28 \\
10 & 135 & 86 & 63 \\
\hline
\end{tabular}
\caption{K nearest neighbor test statistic for malaria cases by \textit{Plasmodium} species, Trinidad, 1968–1997\textsuperscript{*}}
\end{table}

\textsuperscript{*} See Materials and Methods for details.
\textsuperscript{†} $P < 0.05$.
\textsuperscript{‡} $P < 0.01$. 

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure2.png}
\caption{Spatial distribution of malaria cases in Trinidad, 1968–1997 according to parasite species.}
\end{figure}
control around all *P. malaria* cases in the rural areas where bromeliad malaria can occur, and in coastal areas where marshes occur near human habitations. For other imported cases (primarily *P. falciparum* and *P. vivax*) that occur in the cities where the probability of transmission is low, particularly in the dry season, treatment of case and passive surveillance should be the rule.

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Authors’ addresses: Dave D. Chadee, Insect Vector Control Division, Ministry of Health, 3 Queen Street, St. Joseph, Trinidad, West Indies. Uriel Kitron, College of Veterinary Medicine, University of Illinois, 2001 South Lincoln, Avenue, Urbana, IL 61802.

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