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Research Article

Space-Time Cluster Analysis of Malaria in Fars Province-Iran

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Abstract

Background: Malaria, a mosquito-borne infection, is caused by protozoan parasites invading the red blood cells of both humans and animals. Iran is an endemic site for malaria with 1 - 10 cases per one million dwellers, in which 90% of cases occur in southern parts of Iran.
Objectives: to detect space-time clusters of Malaria in Fars province-Iran during 1/1/2011 and 31/12/2015.
Methods: 357 malaria cases were recorded from 19 cities of Fars province. Permutation scan modeling was applied retrospectively to detect the outbreaks of malaria during 1/1/2011 and 31/12/2015. SPSS V. 22, ITSM V. 2002, ArcGIS10, and SaTScan9.4.4 software tools were used. The significance level was considered 0.05.
Results: Based on the results of the current study, 5 space-time clusters were discovered for malaria, indicating that malaria followed a time-space trend in the area (P value < 0.05). The Most Likely Cluster (MLC) contained almost 50% (6/12) of all cases during 1/7/2015 and 31/7/2015 in Firoozabad (P < 0.05); however, non-statistically significant clusters were detected which had clinically important information on the canons of the outbreaks.
Conclusions: Malaria did not occur uniformly in Fars province during 1/1/2011 and 31/12/2015. Detected space-time clusters could help Public health managers and policymakers dedicating clinical staff and facilities to more needy areas and consequently reduce the rate of disease in the area.

Keywords: Malaria, Space-Time Cluster, Scan Statistics, Fars Province-Iran

1. Background

Malaria is a mosquito-borne zoonotic infectious disease caused by protozoan parasites, which invade the red blood cells. The human symptoms include fever, fatigue, headache, nausea, shaking chills, convulsion, coma, abdominal, and muscle pain. The symptoms begin 10-15 days after mosquito bites, which, if left untreated, will recur in successive months (1).

Malaria is more prevalent in tropical and semi-tropical areas, including Sub-Saharan Africa, Asia, and Latin America (2-4). 214 million malaria cases were observed universally, resulting in 434,000 deaths, of which 90% occurred in Africa (5). Iran is as an endemic site for malaria with 519 cases in 2013, from which 80% were vivax (6, 7). Iran showed a 75% reduction in malaria infection between 2000 and 2013; however, the incidence rate of malaria was 10 to 100 cases per 100,000 inhabitants. 90% of cases were seen in south-eastern parts, including Sistan and Baluchistan, Hormozgan, Kerman, and Fars provinces. Precipitation and immigratebility of the residential areas are from the most important causes for high prevalence in these parts (8, 9).

Some diseases are recurrent to a specific space and time. The usual way of assessing these variables was to categorize one dimension and analyze it in another dimension or vice-versa. However, modern technologies such as ArcGIS and SaTScan, with which permutation scan modeling was used, have enabled us to investigate the space and time features of these variables at the same time. This work was the first methodology to check the space-time trait of malaria simultaneously and detect the space-time clusters in Fars province-Iran during 2011 and 2015 (10-13).

2. Methods

Time-series data, including 357 malaria cases recorded from 19 cities, were used retrospectively to detect the space-time clusters of malaria in Fars province-Iran during 2011 and 2015. Since it was a retrospective study, no consent form was applied; however, all the ethical steps including data collection and analysis as well as reporting the results were performed in accordance with the standards approved by Ethics Committee of Ministry of Health, Treatment, and Medical Education under ethics number of IR.SUMS.REC.1396.S755.

Median ± IQR (interquartile range), frequency, and relative frequency were used to describe the quantitative and qualitative data, respectively. Kolmogorov-Smirnov, chi-square, Kruskal-Wallis, and space-time permutation scan modeling were used to analyze the data. SPSS V. 22, ITSM 2002, ArcGIS10, and SaTScan9.4.4 software tools were used. The significance level was considered 0.05.

The space-time trait of a variable was evaluated using the space-time permutation model introduced by Kulldorff using permutation scan statistics (10). Finally, only clusters were reported with no geographical overlap. The same analysis was conducted to detect clusters within large clusters.

3. Results

3.1. Descriptive Statistics

357 cases recorded from 19 cities of Fars province during 2011 and 2015 were involved in the study. The minimum number of cases was 0 in Abade, Bavanat, and Fasa, and the largest numbers were in Shiraz 63.9%, Jahrom 11.2%, Larestan 7.8%, and Kazeroun 5%, respectively.

3.2. Time Trend

A quadratic trend was seen in the annual rates of malaria cases during 2011 and 2015 in Figure 1.

Malaria cases were significantly different over 2011 - 2015 years ($P < 0.05$). The difference was due to the differences observed in 2011 with other years (P value < 0.05 for all).

3.2.1. Monthly Time Trend and Geographical Distribution

Figure 2 shows the monthly trend of malaria cases from January 2011 to February 2015.

Seasonal Auto-Regressive Moving Average, SARMA $(3, 2)_{12}$, model was fitted to explain the trend.

The results indicated significant differences among malaria cases in 12 months of the year ($P < 0.05$) in Table 1. In addition, malaria cases were different in 19 cities of Fars province ($P < 0.05$) in Table 2.

Figure 3 shows the geographical distribution of malaria cases by six different climates of humidity.

3.3. Space-Time Permutation Analysis

In this study, 5 space-time clusters were detected, of which the MLC was statistically significant ($P < 0.05$). MLC contained 1.7% (6/357) of the total cases, and the other four non-significant clusters contained 10.9% (39/357) of the total cases across the study period. Table 3 shows the results of the permutation space-time analysis.

3.3.1. The Most Likely Cluster (MLC)

The MLC occurred in Firoozabad and contained almost 50% (6/12) of all cases during 1/7/2015 and 31/7/2015. The other 50% of malaria cases occurred in Shiraz [2/12 (16.7%)], Larestan [2/12 (16.7%)], Esfahan [1/12 (8.3%)], and Farashband [1/12 (8.3%)] in July 2015.

3.3.2. Secondary Clusters (SCs)

The four SCs encompassed 10.9% (39/357) of the total cases during the study period. SC1 included Kazeroun, which had 100% (6/6) of the cases during 1/8/2015 and 30/11/2015. In this SC, 66.6% (4/6) of the cases occurred in August, 16.6% (1/6) in September, 16.6% (1/6) in November, and 0% in October (0/6).

SC2 had 100% (2/2) of the cases during 1/3/2014-30/4/2014. Among these cases, 50% were in March, and the other 50% were in April.

SC3 composed 96.6% (29/30) of the cases from 1/4/2012 to 31/8/2013. In this SC, Lamerd, Larestan, and Jahrom had 6.6% (2/30), 33.3% (10/30), and 56.6% (17/30) of all the cases, respectively. Indeed, the largest number of cases over 1/4/2012-31/8/2013 were in May [23.3% (7/30)], June [20% (6/30)], April [13.3% (4/30)], August [13.3% (4/30)], September [10%(3/30)], March[6.6% (2/30)], July[6.6% (2/30)], and December [6.6% (2/30)]. However, no cases were detected in October, November, January, and February.

SC4 had 100% (2/2) of all cases on 1/11/2012-31/3/2013. It encompassed Arsenjan and Marvdasht. Arsenjan and Marvdasht had 50% (1/2) of the total cases in that period. In addition, 50% (1/2) of the cases occurred in July, and the other 50% (1/2) occurred in May.

3.3.3. Subcluster Analysis

It was also interesting to determine whether or not there were any significant clusters within the large clusters. In doing so, the sub-cluster analysis was conducted, showing no statistically significant space-time clusters (P value > 0.05). Table 4 shows the results of the sub-cluster analysis.

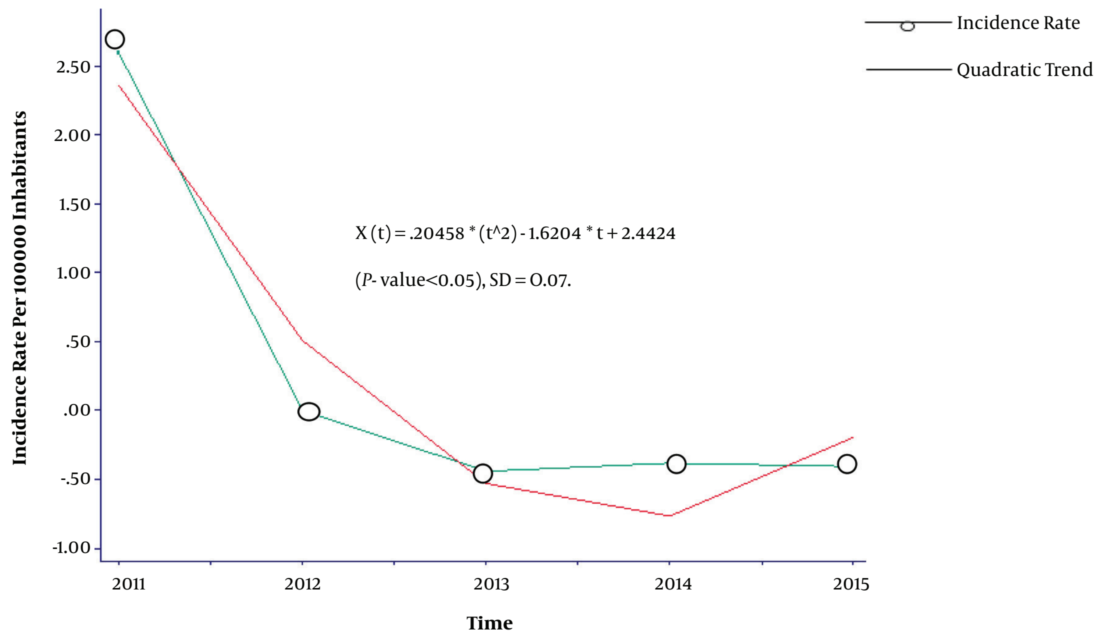

Figure 1. The incidence rate of malaria in Fars province, Iran from 2011 to 2015.

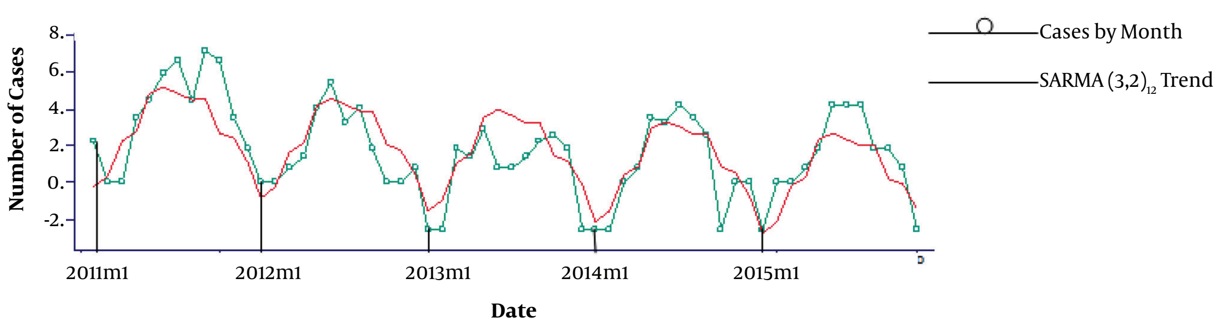

Figure 2. The number of malaria cases by month of year of onset in Fars province- Iran from 2011 to 2015 (m1 is the first month of the year (January).

4. Discussion

The detected space-time clusters showed that malaria followed a space-time feature in the area during 2011 and 2015. 5 clusters were found of which the MLC in Firoozabad as the canonical site for malaria was the only significant cluster. It included 50% of all cases during 1/7/2015 and 31/7/2015. MLC contained almost 1.7% of all cases over the study period. In the current study, the purely temporal analysis revealed an outbreak from June to September (from 2004 to 2006), which was in concordance with the MLC time frame (June (2017)).

Also, the detected time frame of MLC from April 2004 to November (2007) was in agreement with the transmission period of malaria in Fars province (14).

In a study in China, the purely temporal analysis resulted in three clusters happening from March to August (in 2005), from May to October (in 2006), and from March to April (2007). These periods encompassed the transmission period of malaria mainly from April to November. In addition, space-time clustering in the current study detected three clusters, including MLC occurring in 1/1/2005–31/5/2007, one SCs in 1/2/2005–28/2/2007, and another SCs in 1/1/2005–31/1/2005. All these periods covered the transmission time of malaria and proved the efficacy of this methodology on malaria (15).

In a previous study done on cutaneous leishmaniasis

Table 1. Comparison of Malaria Cases in 12 Months in Fars Province, Iran During 2011 – 2015[a]

	January	February	March	April	May	June	July	August	September	October	November	December
January						0.006	0.009	0.037	0.037			
February					0.042	0.004	0.005	0.025	0.025			
March						0.01	0.013					
April						0.037	0.047					
May		0.042										
June	0.006	0.004	0.01	0.037							0.029	0.007
July	0.009	0.05	0.013	0.047							0.037	
August	0.037	0.025										0.042
September	0.037	0.025										0.042
October												
November						0.029	0.037					
December						0.007		0.042	0.042			

[a] Values are statistically significant at 0.05 level.

Table 2. Comparison of Malaria Cases in 19 Cities of Fars Province- Iran During 2011 – 2015[a]

	Arsenjan	Stahban	Eghlid	Abade	Bavanat	Jahrom	Safashahr	Darab	Sepidan	Shiraz	Farashband	Fasa	Firoozabad	Kazeroun	Larestan	Lamerd	Marvdasht	Mamasani	Neireez
Arsenjan						0.006				0.001					0.025				
Stahban						0.004				0.001					0.013				
Eghlid						0.004				0.001					0.013				
Abade						0.002				0.001					0.007				
Bavanat						0.002				0.001					0.007				
Jahrom	0.006	0.004	0.004	0.002	0.002		0.002		0.004	0.002		0.002				0.01	0.043	0.006	0.006
Safashahr						0.002				0.001					0.007				
Darab										0.001									
Sepidan						0.004				0.001					0.013				
Shiraz	0.001	0.001	0.001	0.001	0.001	0.002	0.001	0.001	0.001		0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001
Farashband										0.001									
Fasa						0.002				0.001					0.007				
Firoozabad										0.001									
Kazeroo										0.001									
Larestan	0.025	0.013	0.013	0.007	0.007		0.007		0.013	0.001		0.007				0.046		0.025	0.025
Lamerd						0.01				0.001					0.046				
Marvdasht						0.043				0.001									
Mamasa						0.006				0.001					0.025				
Neireez						0.006				0.001					0.025				

[a] Values are statistically significant at 0.05 level.

Table 3. The Results of Space-Time Permutation Analysis on Malaria Cases in Fars Province- Iran During 1/1/2011-31/12/2015

Cluster	Location(s)	Radius(km)	Observed/Expected	Time Window	Test Statistics	P-Value[a]
Cluster 1	Firoozabad	0	26	1/7/2015 to 31/7/2015	13.71	< 0.0001
Cluster 2	Kazeroon	0	5.41	1/8/2015 to 30/11/2015	5.27	0.2389
Cluster 3	Darab	0	26.44	1/3/2014 to 30/4/2014	4.63	0.47
Cluster 4	Lamerd, Larestan, Jahrom	136.2	1.82	1/4/2012 to 31/8/2013	4.57	0.48
Cluster 5	Arsenjan, Marvdasht	46.29	12.75	1/11/2012 to 31/3/2013	3.25	0.96

[a] Statistical significance was evaluated using Monte Carlo hypothesis testing.

(CL), a disease with a very high prevalence in Fars province resulted in discovering space-time clusters in the area. it showed that permutation scan modeling was efficient enough in detecting outbreaks of infectious diseases in the area (11-13).

Unlike our quadratic trend of malaria during 2011 and

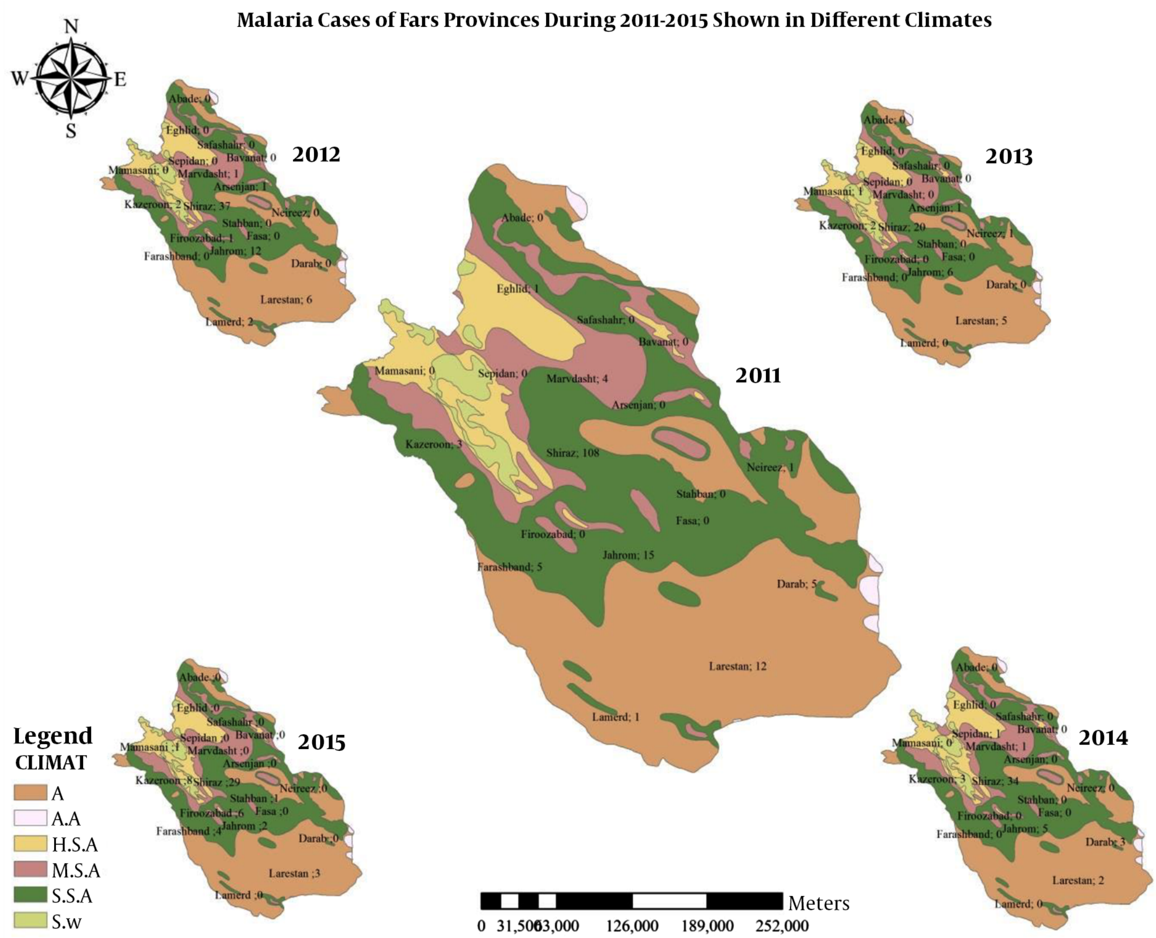

Figure 3. The geographical distribution of malaria cases in Fars province-Iran during 2011 - 2015 in six different climates. Note: Six climatic categories based on the humidity of the area are shown in different colors.

Table 4. The Results of Sub-Cluster Analysis on the Detected Clusters of Malaria in Fars Province from 1/1/2011 to 31/12/2015

Cluster	Location	Radius (Km)	Start Date	End Date	Test Statistic	Observed/Expected	P-Value[a]
Cluster 1	Lamerd	0	1/6/2012	31/12/2012	1.27	3.94	0.61
	Larestan	0	1/5/2011	30/9/2011	1.02	1.58	0.89
Cluster 2	Arsenjan	0	1/3/2012	31/3/2013	0.83	2.67	0.18

[a] Statistical significance was evaluated using Monte Carlo hypothesis testing.

2015 in Fars province, some studies showed a decreasing trend over time, especially in vivax malaria (15-17).

Clinical and statistical preferences have always been controversial; permutation scan statistics results in statistically significant and non-significant clusters. Non-significant clusters are clinically canons of infection. Methodologically, it is a drawback in permutation scan modeling. As a solution, Population Attributable Risk (PAR) could help to decide between clinical and statistical significant clusters. PAR is a value between 0 and 1, and the closer this number is to one, the more likely it is to be a real cluster (15). Another limitation was that the surveillance system in Iran was passive. For example, many patients did not go to the health centers, and consequences were not registered in the health system; this leads to underestimating the disease prevalence. Finally, there was a variety of meteorological factors in Fars province, such as precipitation and wind velocity, which were not included in the study. The sero-epidemiological traits of reservoirs and agents and hosts' genetic features were not considered as well.

Although the data were old, it was the first methodology evaluating space and time traits of malaria in the south of Iran. Mathematically, it was shown that malaria did not follow the uniform distribution over time and space in the area, and space- time clusters could function as an early warning system to the health system. In other words, the findings could be useful in organizing the priorities of facilities in high-risk areas.

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Footnotes

Authors' Contribution: Marjan Zare: data gathering, data analysis, manuscript writing, manuscript editing, presenting the results, reading and approving the manuscript. Abbas Rezaianzadeh: manuscript editing, presenting the results, reading and approving the manuscript. Mohsen Aliakbarpoor: data gathering, clinical tests, patient registry, spatial layers provider, reading, and approving the manuscript. Hossain Faramarzi: clinical tests, patient registry, reading and approving the manuscript, clinical counseling. Mostafa Ebrahimi: clinical tests, patient registry, reading and approving the manuscript. The manuscript has been read and approved by all authors, the authorship criteria have been met by all authors, and the manuscript presents an honest academic work.

Conflict of Interests: There is no conflict of interest.

Ethical Approval: All ethical steps, including data collection and analysis as well as reporting the results, were in accordance with the standards approved by the Ethics Committee of the Ministry of Health, Treatment, and Medical Education under ethics number: IR.SUMS.REC.1396.S755. Indeed, the process of work was completely anonymous and the results were reported to the study participants.

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