Investigating spatio-temporal distribution and diffusion patterns of the dengue outbreak in Swat, Pakistan

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\textbf{A B S T R A C T}

\emph{Introduction:} Dengue has been endemic to Pakistan in the last two decades. There was a massive outbreak in the Swat valley in 2013. Here we demonstrate the spatio-temporal clustering and diffusion patterns of the dengue outbreak.

\emph{Methods:} Dengue case data were acquired from the hospital records in the Swat district of Pakistan. Ring maps visualize the distribution and diffusion of the number of cases and incidence of dengue at the level of the union council. We applied space-time scan statistics to identify spatio-temporal clusters. Ordinary least squares and geographically weighted regression models were used to evaluate the impact of elevation, population density, and distance to the river.

\emph{Results:} The results show that dengue distribution is not random, but clustered in space and time in the Swat district. Males constituted 68\% of the cases while females accounted for about 32\%. A majority of the cases (>55\%) were younger than 40 years of age. The southern part was a major hotspot affected by the dengue outbreak in 2013. There are two space-time clusters in the spatio-temporal analysis. GWR and OLS show that population density is a significant explanatory variable for the dengue outbreak, while GWR exhibits better performance in terms of $R^2 \sim 0.49$ and AICc $\sim 700$.

\emph{Conclusion:} Dengue fever is clustered in the southern part of the Swat district. This region is relatively urban in character, with most of the population of the district residing there. There is a need to strengthen the surveillance system for reporting dengue cases in order to respond to future outbreaks in a robust way.

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\textbf{Introduction}

Dengue fever is an arboviral disease caused by the dengue virus (DENV). DENV belongs to the \textit{Flavivirus genus} within the \textit{Flaviviridae} family and has four distinct serotypes, DEN-1, DEN-2, DEN-3, and DEN-4, with each serotype found alone in most cases and, rarely, as co-infection [1,2]. Dengue is present in more than 128 countries around the globe, and more than 4 billion people are at risk of dengue infection [3,4]. About one third of the world’s population inhabit a country at risk of dengue fever, with the majority residing in developing countries [5]. Currently dengue is a major threat to tropical and subtropical countries. However, dengue is expanding to other regions such as Europe, which are not located in tropical or subtropical regions, because of increased international travel [6].

Dengue virus is emerging in new areas and regions, which could be attributable to a suitable habitat for the vector, rapid urbanization [7], increased international travel, climate change, and local and regional climatic phenomena [8]. Dengue virus infection is usually asymptomatic but can develop into cases presenting symptoms ranging from a mild fever to potentially fatal dengue shock syndrome [9]. The transmission of the dengue virus can occur...
at the same time as other Flavivirus viruses, such as the zika or chikungunya virus, leading to an ambiguous diagnosis or combined infections [10,11].

*Aedes aegypti* and *Aedes albopictus* are the two important vectors involved in dengue transmission. These vectors are widely present in tropical and subtropical countries located in Africa, Asia, Australia, the Americas, and the Middle East [12]. *Ae. aegypti* is the primary vector of the dengue, yellow fever, and chikungunya viruses, and is broadly found in the subtropics and tropics [13]. The Indian sub-continent is at risk of vector-borne diseases like malaria and dengue. Although incidences of malaria have dropped since 1990, dengue has appeared and is continuously increasing in the region [14]. *Ae. aegypti* is an urban mosquito and likes to dwell and breed in artificially created habitats rather than natural environments [15,16].

There are many drivers which impact the spread of dengue by affecting the behavior and life-cycle of vectors. Temperature changes and rainfall patterns [17] in the locality, along with regional climate phenomena like the El Niño Southern Oscillation (ENSO) and the Indian Ocean Dipole (IOD), have been found to have an influence in this regard [18–20]. It is postulated that the ENSO phenomenon has an impact on the redistribution, intensification, and generation of several vector-borne diseases.

Higher temperatures can reduce larval development time and the extrinsic incubation period (EIP) of a virus [21,22]. Precipitation plays an arbitrary role on vector ecology: rainfall is required to create mosquito habitats but extreme rainfall has the effect of killing the larvae and adult mosquito [23]. Generally speaking, an increase in rainfall and temperature, as well as humidity, could lead to an increased risk of dengue transmission [24–26]. In addition to climate parameters, population density and lower socioeconomic indicators are also positively linked to dengue incidence [27,28]. Higher population density is associated with an increase in dengue incidence, as observed in several countries [29,30].

Pakistan has experienced several dengue outbreaks since it was first reported in 1994 [31]. Since then it has experienced sporadic cases of dengue in other parts of the country. The four serotypes of DENV have been identified in outbreaks in Pakistan [32]. In an outbreak in Karachi, Pakistan’s largest metropolitan city and economic hub, DEN-2 and DEN-3 were identified as the prevalent serotypes [33]. However, in the 2011 outbreak in Lahore city, DEN-2 was the dominant serotype, and DEN-3 and DEN-4 contributed to fewer infections [34]. The first outbreak in Lahore city occurred in 2006, and later spread to the other cities of the Punjab province over a period of 5 years. This led to the largest outbreak of 2011, in which more than 20,000 cases were reported along with more than 360 deaths across the province [35,36].

Recently, geographical information system (GIS) and other related tools have been used in vector-borne disease surveillance and control. Several studies have reported the geographical distribution of dengue outbreaks in space and time along with prospective hotspot predictions [37,38]. Spatial ring maps are a novel way of displaying the spatio-temporal diffusion patterns of disease outbreaks and crimes [39]. These are important tools in spatial epidemiology. GIS and related tools help to identify the spatial targets of intervention to effectively combat the spread of the disease.

The Swat valley in Pakistan experienced an unprecedented outbreak in 2013 [40]. No dengue outbreak had been recorded in this region before 2013, probably due to surveillance data not being available. Here we visualized the geographical distribution of dengue in the Swat district at the union council level, which is the smallest administrative unit in Pakistan. To the best of our knowledge no other research has investigated the spatio-temporal distribution of the 2013 dengue outbreak in the Swat district at the level of the union council. We applied spatial scan statistics and a spatial regression model to reveal spatio-temporal clusters and the related risk factors at the union council level in the Swat district.

**Materials and methods**

**Study area**

The Swat district is located in Khyber Pakhtunkhwa near the Pakistan–Afghanistan border (Fig. S1). The Swat valley is situated in the north of Khyber Pakhtunkhwa, at 35° north latitude and 72° east longitude, and is enclosed by mountains. The Swat district varies in average elevation from 770 m in the Barikot union council to around 4000 m in the Kalam union council. The high altitude of the Swat valley means that it enjoys very pleasant weather, which attracts large numbers of tourists from across the country. Swat is situated in the temperate zone. June is the hottest month, and has mean maximum and minimum temperatures of 33 °C and 16 °C respectively. January is the coldest month, with average temperatures ranging from 11 °C to −2 °C. Around 1.3 million people live in the Swat valley area, which includes the valleys of Chitral and Gilgit–Baltistan in the north, the Dir valley in the west, and the Mardan valley in the south [40]. The Indus River separates it from the Hazara division in the east. The Swat district is divided into 65 administrative units, known as union councils, as shown in Fig. S1.

**Data source**

The confirmed dengue case data for the study area were collected from the district health office in the Swat district. Positive cases were confirmed following detection of the nonstructural protein 1 or anti-dengue IgM by an enzyme-linked immunosorbent assay (ELISA). Age, gender, and location of the cases were recorded in the data at the time of patient admission to a health facility. Population figures have been extracted from the district health profile of Swat published by PAIMAN (Pakistan Initiative for Mothers and Newborns) and sponsored by the United States Agency for International Development (USAID).

**Spatio-temporal cluster analysis**

The number of dengue cases and incidence (both monthly and weekly) were calculated, and ring maps were plotted to visualize the diffusion patterns of dengue cases in space and time following the method developed by Chan et al. [39]. The space-time analysis was carried out by SaTScan version 9.4.2 to detect spatial and temporal clusters of dengue transmission [41]. A space-time permutation model was used to detect clusters across space/time by comparing the disease risk within and outside the scanning windows. Clusters with the highest log likelihood ratio (LLR) are considered the most likely clusters. The maximum window size was set as 50% of the population at risk [41]. The p-value was obtained through Monet Carlo simulation to perform hypothesis testing, and the cut-off value is set as 0.05.

**Ordinary least squares (OLS) and geographically weighted regression (GWR)**

Both ordinary least squares (OLS) and geographically weighted regression (GWR) models were applied to assess the impact of elevation, distance to water bodies, and population density on the occurrence of dengue fever. The detailed information and spatial distribution of dependent and independent variables used for OLS and GWR are shown in the supplementary material (Table S1, Fig. S3). OLS was applied to evaluate the global relations between dependent and independent variables. GWR helps to identify the spatial influence on the neighborhoods which are not explained by
OLS [42]. We used cross validation (CV) as the bandwidth method and opted for the adaptive kernel type in our analysis settings for GWR. The adaptive kernel was chosen because the distribution of union councils was heterogeneous in the study area.

The coefficient of determination (R²) and corrected Akaike’s Information Criterion (AICc) were used to compare the model performance of OLS and GWR. Variance inflation factor (VIF) was used to evaluate the extent of multicollinearity among the independent variables. A VIF value greater than 10 indicates strong multicollinearity among the variables. GWR models can be elaborated by the following equation:

\[ y_i = \beta_0 + \sum_{j=1}^{k} \beta_j x_{ij} + \epsilon_i \]

where \( y_i \) signifies the cumulative incidence rate of dengue fever in 2013 at union council \( i \); \( u_i \) and \( v_i \) are centroid coordinates for union council \( i \); \( x_{ij} \) represent a set of \( k \)-independent variables (where \( j = 1, \ldots, k \)); and \( \beta_0 \) and \( \beta_j \) are coefficient estimates for the corresponding location. The map layout was performed by ArcGIS 10.3 (ESRI, Redland, CA).

### Results

A total of 9032 confirmed cases of dengue fever were reported in the Swat district in 2013 (Table 1). The outbreak started in August 2013, reached its peak in September, and subsided in December (Fig. S2). The infection was dominant among males (68%) while females accounted for about 32%. The majority of the cases (>55%) were younger than 40 years of age.

The spatial and temporal diffusion visualization indicates that dengue cases started to emerge in mid-August and subsided by mid-November (Fig. 1). The first dengue cases began to appear in week 34 in the union councils located in the southern part of the Swat district and spread to the surrounding regions between weeks 36 and 47. As indicated by the ring map, two union councils did not report any dengue cases, even though they are located in the central part of the district, which could be because of missing data or a reporting error.

Fig. 2(A) demonstrates the spatial distribution of dengue incidence in each union council of the Swat district. The dengue hotspot is mainly clustered in the southern part of Swat, which is more urban and is home to a major chunk of the Swat population. There are 16 union councils included in the primary cluster, Rahim Abad, Shahdara Nawam Kalay, Banringaro Darai, Amankot Faiz Abad, Malakanan Landakass, Malok Abad, Rang Muhallah, Gulkada, Saidu Sharif, and Qamber (Fig. 2(B)). The temporal distribution of the first cluster, which is from 8/22 to 10/30, almost spanned the whole transmission season (Table 2). The secondary cluster covered a larger area (radius = 29.88 km), which includes 32 union councils with shorter temporal clusters (9/7–9/22).

Three risk factors were analyzed using OLS and GWR (Tables 3 and 4). The global regression (OLS) model demonstrates that population density and distance to river are positively associated with dengue incidence in the Swat district; however, only population density reached statistical significance (Table 3). Dengue incidence decreased with an increase in elevation in the study area.

The GWR model showed the detailed spatial distribution of the associations between dengue incidence and risk factors in the Swat district (Fig. 3). The correlations showed high variability in terms of space. Overall, population density showed a strong correlation with dengue incidence in the south and southwestern areas, with distance to river only positively associated with dengue incidence in the south (Fig. 3B and C). Elevation is negatively associated with dengue fever near the hotspot region but the effect was inverse in the north (Fig. 3D). The local R-squared indicates that the GWR model performed better in the southwestern region of the Swat district (Fig. 3A).

The GWR model exhibited better model performance than the OLS model in the study (AICc: 700.52 V.S.7188.85). The higher R² value (0.49) also supports the fact that GWR can better explain the associations between dengue incidence and risk factors after accounting for spatial autocorrelation. No spatial autocorrelation can be detected among the standardized residuals of the GWR model (Moran’s I test: z-score = -0.54, P = 0.58).

### Discussion

This study attempts to investigate the spatio-temporal distribution of the 2013 dengue outbreak in the Swat district. This is

### Table 1
Demographic characteristics of dengue cases in Swat, 2013.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Number of case</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>6157</td>
<td>68.2</td>
</tr>
<tr>
<td>Female</td>
<td>2875</td>
<td>31.8</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;10</td>
<td>358</td>
<td>3.9</td>
</tr>
<tr>
<td>11–20</td>
<td>1767</td>
<td>19.6</td>
</tr>
<tr>
<td>21–30</td>
<td>1969</td>
<td>21.8</td>
</tr>
<tr>
<td>31–40</td>
<td>1241</td>
<td>13.7</td>
</tr>
<tr>
<td>41–50</td>
<td>678</td>
<td>7.5</td>
</tr>
<tr>
<td>51–60</td>
<td>369</td>
<td>4.1</td>
</tr>
<tr>
<td>61–70</td>
<td>153</td>
<td>1.7</td>
</tr>
<tr>
<td>&gt;70</td>
<td>70</td>
<td>0.8</td>
</tr>
<tr>
<td>Missing</td>
<td>2426</td>
<td>26.9</td>
</tr>
<tr>
<td>Total</td>
<td>9032</td>
<td>-</td>
</tr>
</tbody>
</table>

### Table 2
Spatio-temporal clusters of dengue fever in the Swat district.

<table>
<thead>
<tr>
<th>Cluster type</th>
<th>Radius</th>
<th>Time frame</th>
<th>Observed</th>
<th>Expected</th>
<th>RR</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary</td>
<td>11.26 km</td>
<td>8/22–10/30</td>
<td>5267</td>
<td>299.26</td>
<td>17.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Secondary</td>
<td>29.88 km</td>
<td>9/7–9/22</td>
<td>337</td>
<td>135.73</td>
<td>2.48</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

### Table 3
Summary of the ordinary least squares (OLS) regression model.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Estimates</th>
<th>Standard error</th>
<th>p-value</th>
<th>VIF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>15.65</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Population density</td>
<td>0.03</td>
<td>0.07</td>
<td>0.0001</td>
<td>1.32</td>
</tr>
<tr>
<td>Elevation</td>
<td>-0.009</td>
<td>0.03</td>
<td>0.75</td>
<td>8.21</td>
</tr>
<tr>
<td>Distance to river</td>
<td>0.12</td>
<td>1.12</td>
<td>0.92</td>
<td>8.79</td>
</tr>
<tr>
<td>R-squared</td>
<td>0.37</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AIC</td>
<td>718.85</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

VIF = variance inflation factor.
1 p-Value < 0.05.

### Table 4
Summary of the geographical weighted regression (GWR) model.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Minimum</th>
<th>25% quartile</th>
<th>50% quartile</th>
<th>75% quartile</th>
<th>Maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>-51.27</td>
<td>18.22</td>
<td>74.91</td>
<td>138.01</td>
<td>201.12</td>
</tr>
<tr>
<td>Population density</td>
<td>0.01</td>
<td>0.02</td>
<td>0.03</td>
<td>0.03</td>
<td>0.05</td>
</tr>
<tr>
<td>Elevation</td>
<td>-0.15</td>
<td>-0.1</td>
<td>-0.06</td>
<td>-0.016</td>
<td>0.03</td>
</tr>
<tr>
<td>Distance to river</td>
<td>-2.09</td>
<td>-0.35</td>
<td>1.39</td>
<td>3.13</td>
<td>4.87</td>
</tr>
<tr>
<td>Condition number*</td>
<td>14.68</td>
<td>19.21</td>
<td>23.74</td>
<td>28.27</td>
<td>32.79</td>
</tr>
<tr>
<td>R-squared</td>
<td>0.49</td>
<td></td>
<td></td>
<td></td>
<td>700.52</td>
</tr>
</tbody>
</table>

* condition number: if the value is larger than 30, it indicates multicollinearity.
the first study to analyze dengue transmission at the union council level, which is the smallest administrative unit in Pakistan. There is a dearth of literature on the 2013 dengue outbreak in terms of spatio-temporal and diffusion patterns. The majority of other investigations focused on its demographical, clinical, serological, and epidemiological features [43–46].

It is worth noting in terms gender distribution that dengue incidence is much higher among males. This is a unique finding compared with other studies, which indicate no significant gender difference among dengue cases [3,47,48]. However, a previous study in the Lahore district, the dengue hotspot of the Punjab province of Pakistan, supports our observation [8]. This finding is also in line with the study on dengue in Jeddah, Saudi Arabia [38]. This could be attributable to cultural practices, as females mostly wear full sleeves and long attire in Pakistan. The majority of females have relatively little chance to be exposed to the open environment.

Fig. 1. Space-time diffusion patterns of dengue fever in Swat.
Fig. 2. Dengue incidence rate (A) and spatio-temporal clusters (B) in Swat.
The green circle indicates the union councils in the primary cluster while the red color indicates the secondary cluster.
because they contribute less to the workforce in urban areas. By contrast, males, being the breadwinners, have more chance to be exposed at dawn and dusk while going to and from work. Dawn and dusk are the prime biting times of *Aedes* mosquitoes.

A previous study indicated that the introduction of dengue in 2013 and its subsequent spread across the Swat district could be attributed to an outbreak in the southern part of the country, i.e. in the Punjab region [49]. The study looked at the impact of human mobility on the transmission of dengue across Pakistan, and proposed that the dengue outbreak in Lahore could have triggered the dengue outbreak in Swat. On the other hand, the disease vectors, *Ae. albopictus* and *Ae. aegypti*, are also available in the Swat district [43]. When the environmental conditions are suitable for mosquito propagation, the introduced virus could maintain its transmission in the Swat district and cause the subsequent outbreak. It should be noted that the Swat area, by virtue of its high elevation and cooler, pleasant weather in the summer season, attracts many tourists from other regions, including the Punjab area, during the summertime. Thus, travel activity could play an important role in the introduction of the dengue virus if the outbreak has occurred in other areas.

Our study identified two significant spatio-temporal clusters of dengue incidence in Swat, and the hotspots could be associated with other environmental risk factors. Population density has been shown to be an important factor for dengue transmission because the vector prefers to inhabit surrounding urban regions [50]. It should be noted that the union councils in the northern part of the Swat district have an average elevation of 2000–4000 m, which is not suitable for the mosquito vector to survive [51,52]. Whether the presence of fewer dengue cases in areas of higher elevation is attributable to the extended habitat suitability of the mosquito vector caused by climate change require further investigation. The spatio-temporal spread of dengue infection in three different cities of Pakistan has been discussed by Fareed et al. [53]. The study indicated that, along with environmental factors, land cover and land use (LCLU) changes in Rawalpindi, Islamabad, and Swat also contributed to the spread of dengue. They are of the view that urbanization, housing density, LCLU, housing type, indoor–outdoor, and breeding sites form a complex structure which promotes dengue occurrence and subsequent transmission. The next step is to explore the impact of landscape-level factors, along with climate conditions, on dengue transmission and

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**Fig. 3.** GWR results of R-squared (A), coefficient of distance to river (B), population density (C), and elevation (D).
vector ecology in the Swat district. This study revealed the preliminary finding that dengue is clustered in a specific space and time, which would enable the health authorities to put in place more control or prevention measures around these regions.

This study has several limitations. First, asymptomatic infection is not included in the analysis, which could result in the underestimation of disease transmission. Detecting asymptomatic dengue cases would require a comprehensive community-level serological survey that is not available in the Swat district. Second, there is a lack of a systematic data collection, diagnostic, and reporting procedures countrywide, which also cause a certain level of underreporting. For instance, the ratio of suspected cases without a confirmed diagnosis is needed to understand the diagnostic capacity in different health clinics. Government authorities need to develop a standard operational procedure to enhance the reliability of dengue surveillance systems in Pakistan. Third, vector data is not available in the Swat district. Ae. albopictus and Ae. aegypti have different behavioral and ecological characteristics. An investigation into the influence of climate or other environmental factors on mosquito abundance and infection, in light of the behavior of vector mosquitoes, is urgently required in this region.

It is critical to develop a dengue early-warning system to confront climate/environmental changes in the near future, and community health education needs to be designed simultaneously to enhance knowledge and awareness of dengue risk among the general population. In the short term, there is a need to strengthen surveillance systems and put in place vector control strategies that combat potential outbreaks effectively.

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Competing interests

None declared.

Ethical approval

Not required.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.jphe.2017.12.003.

References


