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

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A B S T R A C T

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.
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.
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 '$R^2 = 0.49$ and AICc = 700'.
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 here. There is a need to strengthen the surveillance system for reporting dengue cases in order to respond to future outbreaks in a robust way.

Introduction

Dengue fever is an arboviral disease caused by the dengue virus (DENV). DENV belongs to the *Flavivirus genus* within the *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

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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