Title: Space-time clusters of dengue fever in Bangladesh

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Summary

OBJECTIVE: To examine the space-time clustering of dengue fever (DF) transmission in Bangladesh using geographical information system and spatial scan statistics (SaTScan).

METHODS: We obtained data on monthly suspected DF cases and deaths by district in Bangladesh for the period of 2000-2009 from Directorate General of Health Services. Population and district boundary data of each district were collected from national census managed by Bangladesh Bureau of Statistics. To identify the space-time clusters of DF transmission a discrete Poisson model was performed using SaTScan software.

RESULTS: The results indicate that space-time distribution of DF transmission was clustered during three different periods 2000-2002, 2003-2005 and 2006-2009. Dhaka was identified as the most likely cluster for DF in all three periods. Several other districts were identified as significant secondary clusters. However, the geographic range of DF transmission appears to have declined in Bangladesh over the last decade.

CONCLUSION: There were significant space-time clusters of DF in Bangladesh over the last decade. Our results would prompt future studies to explore how social and ecological factors may affect DF transmission and would also be useful for improving DF control and prevention programs in Bangladesh.

Introduction

Dengue fever (DF) is one of the most important emerging arboviral diseases worldwide (WHO 2000). The virus is transmitted through the bite of container breeding mosquitoes *Aedes aegypti* and *Aedes albopictus* which are present in most tropical and subtropical countries (Rigau-Perez *et al.* 1998). Symptoms of DF infections in human vary from mild flu like DF to life threatening dengue hemorrhagic fever (DHF) or dengue shock syndrome (DSS)(Gubler 2002). It has been estimated that about 50 million people worldwide become infected with dengue virus annually. Globally, the geographic range of DF transmission has increased dramatically in recent years (WHO 2000). It has been hypothesized that many social and demographic changes such as population growth, urbanization, air travel and climate change contribute to the increased incidence and geographical expansion of DF transmission (Gubler 2002;Wu *et al.* 2007).

DF has become a serious public health concern in Bangladesh after the first large scale outbreak occurred in 2000. However, evidence suggests that sporadic DF outbreaks occurred in Bangladesh between 1964 and 1999 (Hossain *et al.* 2003;Rahman *et al.* 2002). Since 2000, DF cases have been reported every year in all major cities of Bangladesh. More than 23,872 cases were reported to the Directorate General of Health Services (DGHS) and 233 were fatal between 2000 and 2009. The worst outbreak was in 2002 with 6,132 cases and 58 deaths. Both *Aedes aegypti* and *Aedes albopictus* were identified as potential vectors for DF transmission in Bangladesh (Ali *et al.* 2003). A national guideline based on the WHO protocol was developed by DGHS in 2000 to control DF transmission and reduce its morbidity and mortality (DGHS 2000).

In absence of effective vaccine and specific treatment, vector control is the only way to prevent DF transmission. Previous studies suggest that the risk of DF transmission varies over space and time (Mammen *et al.* 2008;Thai *et al.* 2010;Tran *et al.* 2004). Therefore, an identification of high risk areas can be useful for prioritizing DF surveillance and vector control efforts in areas where they are most needed (Ali *et al.* 2003). In this study, we investigated the spatial and temporal distribution of DF at a district level in Bangladesh during 2000 - 2009. Our aim was to identify high risk clustering areas for DF transmission in Bangladesh using space-time scan statistics and geographic information system.

Methods

Study area

Bangladesh is located in South Asia between latitude of 20-27^{o}N and longitude of 88-93^{o}E. It is a low-lying, riverine country with a large marshy jungle coastline of 710 km on the northern littoral of the Bay of Bengal. It is one of the most densely populated countries (density 964.42/km2) in the world and covers 147,570 km^{2}. Bangladesh is divided into seven administrative divisions and these are subdivided into districts. There are 64 districts in Bangladesh, each further subdivided into Upazila or Thana. Dhaka is the capital and largest city of Bangladesh. Other major cities include Chittagong, Khulna, Rajshahi, Sylhet and Barisal. Bangladesh has a tropical monsoon climate characterized by wide seasonal variation in rainfall, temperatures and humidity. Regional climatic differences in this flat country are minor. Four seasons are generally recognized; hot (21.7^{0}C-35.5^{0}C), muggy summer from June to August; humid and rainy autumn from September to November; cool (11.7^{0}C - 26.8^{0}C) and dry winter from December to February; and warm spring from March to May. About 80 % of Bangladesh's rain falls during the wet monsoon season from June to November.

Data collection

As DF is a notifiable disease in Bangladesh, any DF case detected based on the "clinical case definitions" of National guidelines for clinical management of dengue syndrome must be reported to the DGHS through the Civil Surgeon of the district. A DF suspected case is defined by the presence of acute fever accompanied by any two of the following clinical symptoms such as headache, myalgia, arthralgia, rash, positive tourniquet test and leucopenia, absence of any other febrile illness and high index of suspicion based on period, population and place (DGHS 2000). We obtained computerized datasets containing the number of monthly suspected DF cases and deaths by district in Bangladesh for the period of 1 January 2000 to 31 December 2009 from DGHS. There has been no significant change in the dengue reporting system since 2000 in Bangladesh. Relevant population data and electronic boundaries of each district were retrieved from the national census database managed by Bangladesh Bureau of Statistics (BBS). District information includes district name, code, area (km^2), digital boundaries and base maps. The district population were generated from the 2001 and 2010 census data and for the remaining years, the district population were estimated based on linear interpolation (Kulldorf 2010). This study was approved by the Human Research Ethics Committee, Queensland University of Technology.

Statistical analysis

A space-time statistical analysis was applied to detect high risk clusters of DF using SaTScan software (version 9). Case files generated using monthly aggregated numbers of DF cases for each district was used in data analysis. Population and coordinates data were also used as inputs in SaTScan. We fit a discrete Poisson regression model to identify space-time clusters after adjustment for the uneven geographical density of district population (Kulldorf 2010;Kulldorf *et al.* 1998).

For cluster specification in space-time analyses, three parameters were set for cluster size: the maximum circle radius in the spatial window, maximum temporal window and the proportion of the population at risk. Of the 64 districts 99% of them were within a 40 km radius. Thus, 40 km was chosen as the maximum circle radius for all analyses. Space-time analyses were also performed using 10 km, and 20 km of maximum circle radius and the results obtained were very similar to those using 40 km. The analyses were conducted using a maximum spatial cluster size of 50% of the population at risk in the spatial window and a maximum of 50% of the study period in the temporal window. Because of the differences in population densities across Bangladesh, it was decided to limit the spatial cluster size to 50% of the population at risk. The spatial clusters were also defined to cover less than 25% and 10% of total population at risk and similar results were obtained to the 50% of the population limit, which suggests that the maximum cluster size is adequate to be limited by 50% of the population at risk. The most likely and secondary likely clusters were detected through the likelihood ratio test. Significance of the clusters was evaluated with Monte Carlo simulation which was set to 9999. MapInfo Professional (version 10.0) was used to display space-time clusters.

Results

DF epidemics and outbreaks

The epidemic pattern of DF fluctuated from 2000 to 2009 with major outbreaks in 2000 and 2002 (Figure 1). The monthly number of DF cases ranged from 0 to 3,281 (mean = 197.7, standard deviation = 454.05) and the highest number of cases was reported in August 2002. DF outbreaks in Bangladesh after 2002 showed a decreasing trend. Although DF outbreaks were regular in Bangladesh, a one year inter-epidemic period between outbreaks was apparent. The monthly number of DF deaths ranged from 0 to 33 and no death was recorded after 2006. Figure 1 also shows a striking variation in monthly numbers of districts with DF infection from 2000 to 2009. Peaks in DF cases generally coincided with high monthly numbers of districts with DF.

Disease clusters

The cluster analyses show that the space-time distribution of DF was clustered during three different periods 2000-2002, 2003-2005 and 2006-2009. Using the maximum spatial cluster size of 50% of the population at risk and a circle radius of 40 km, Dhaka district was identified as the most likely cluster and Khulna and Chittagong as secondary clusters (Figure 2). Another two districts (Barisal and Jhenaidah) were identified as secondary clusters in 2000 during August to October but those clusters were not found in later years (Figure 2). All clusters were identified between June - November which represents a rainy monsoon season in Bangladesh.

Table 1 shows the names of districts included in each cluster, radius (km), observed cases, expected cases, Relative Risk (RR) and log-likelihood ratio. The highest risk for the most likely cluster (Dhaka) was found in 2004-2005 during June - November (RR= 233.3, $p < 0.05$) and the risk was attenuated in 2006 during June -November (RR=119.8, $p < 0.05$) and was lowest in 2000-2002 (RR= 43.48, $p < 0.05$). For secondary clusters the RR ranged from 2.56 to 21.63 and the highest risk was identified for Khulna in 2000 during August - November (RR= 21.64, $p < 0.05$) which reduced to 9.53 in 2006 - 2009.

Spatial dispersion of DF

We attempted to identify whether changes in DF transmission varied with latitude and longitude of district centroids in the periods 2000-2002, 2003-2005 and 2006-2009. A logistic regression model was constructed with the dichotomous outcome variable defined as whether or not an increase of DF cases occurred in each district between the three periods. Longitude and latitude of district centroids were entered as explanatory variables. The results indicate that changes of DF transmission were not significantly associated with geographic variation (i.e latitude and longitude) during 2000-2002, 2003-2005 and 2006-2009.

Discussion

The results of this study indicate a significant variation in spatiotemporal distribution of DF in Bangladesh. The geographic extent of notified DF cases has declined in Bangladesh over the study period. Dhaka was identified as the highest risk area for DF transmission in Bangladesh.

Space-time cluster analysis is a valuable tool to examine how spatial patterns change over time. This study shows that DF transmission in Bangladesh was clustered in three different periods and provides a clear pattern of DF clustering within this country. Dhaka was identified as the most likely cluster for DF transmission. It may be because Dhaka is the largest city in Bangladesh with a high population density. DF can be easily transmitted by mosquitoes in this area. Several other districts (Chittagong and Khulna) in the southern part of the country were identified as secondary clusters (Figure 1). These are also the fastest growing cities located close to seaport and airport. Apart from population density, the movement of infected individuals and/or mosquitoes into this region from overseas through air travel or by ship may increase the chance of DF transmission (Sutherst 2004). However, rainwater collection for domestic purposes is not a common practice in Bangladesh, about 35.5% household of the southwest coastal region of the country found to use rainwater due to arsenic contamination in the ground water and high salinity problem (Ferdausi and Bolkland 2000). The storage of rainwater in uncovered containers in this area might increased the risk of DF transmission by providing suitable mosquito breeding habitat (Beebe *et al.* 2009). Climatic variation and socio-economic factors may also play an important role in promoting DF transmission (Hu *et al.* 2011;Hu *et al.* 2012). Further investigation in these high risk areas is required to understand the dynamics of DF transmission and to discover the role of biological, social and environmental factors in the transmission of DF.

We found that the geographic range of DF clusters has declined in Bangladesh over the last decade (Figures 2). We speculate that the effective management of DF patients according to the national dengue guidelines and huge public awareness after the first outbreak in 2000 might have helped to reduce DF transmission in Bangladesh (Rahman *et al.* 2002). There is no routine dengue vector control programme in Bangladesh. Though, irregular mosquito control activities exist in some cities in Bangladesh which is not specifically for *Aedes* mosquitoes (Chepesiuk 2003). According to Dhaka City Corporation (DCC), they spray adulticide and larvicide in every summer in the areas with high mosquito population. DCC also sprays insecticide indoor and outdoor in the notified area when a DF outbreak occurs. Besides vector control measures, socio-economic changes, population immunity and changes in viral strain and fitness may also contribute to the decreased DF incidence in Bangladesh (Cummings *et al.* 2009;Podder *et al.* 2006). Further research is needed to identify possible reasons for declining trend of DF in Bangladesh.

Dhaka was constantly identified as the most likely cluster and very few districts were identified as secondary clusters for DF transmission in Bangladesh in recent years. We believe that patients detected with DF in other districts might have acquired infections during their visits to Dhaka and symptoms manifested when they returned to their home districts. Although virus was transmitted to other districts through infected patients, it might not continue its transmission due to the reduced number of vectors and the reduced number of virus populations in the dry season (Aaskov *et al.* 2006;Cummings *et al.* 2004;Williams *et al.* 2010). However, we were unable to identify the origin of DF transmission in Bangladesh and its spreading direction due to the lack of information on patient's location, their movement, demographics and mosquito control activity. This should be a priority for future DF research in Bangladesh.

This is the first study to examine the spatiotemporal pattern of DF in Bangladesh. It has clearly demonstrated the heterogeneity of DF risk at the district level in Bangladesh and revealed the spatiotemporal pattern of DF across the country. As cluster analysis could be an important tool for decision makers to prioritize areas where more surveillance and disease prevention efforts are required, our findings can be useful for the Bangladesh health authority to further improve DF control and prevention strategies. Additionally, the method developed in this study may have wider applications in the field of disease surveillance and risk management.

Our study has three key limitations. Firstly, in our analysis, we used reported cases aggregated at the district level, which prohibits analysis at a higher spatial resolution and may lead to important local clusters being missed out. Secondly, there is likely variation in the quality of the DGHS dengue surveillance data. Underreporting is possible in the DGHS data when people infected by DF have subclinical infection and did not seek for medical attention. Finally, we only identified potential DF clusters in this preliminary study, but did not explore possible risk factors associated with clustering. However, our future research will focus on the investigation of various climatic, ecological, and socio-demographic determinants of DF in clustered areas.

Conclusion

In summary, this study demonstrates that DF transmission in Bangladesh was clustered in different spatial and temporal settings and the geographic distribution of DF appears to have contracted over recent years. The impact of socio-demographic changes and climatic factors on DF transmission in clustered areas remains to be determined. Our findings can be useful for the Bangladesh health authority to further improve DF control and prevention strategies. Additionally, the cluster methods developed in this study may have wider applications in the field of disease surveillance and risk management.

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Conflict of interest

We declare that we have no conflict of interest.

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Figure1. Monthly number of DF cases, deaths and districts with DF notification between January 2000 and December 2009 in Bangladesh.

Figure 2. Space-time clusters of DF identified in three different periods in Bangladesh.

Table 1. Space-time clusters of DF in Bangladesh, 2000-2009.