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Spatial and population drivers of persistent cholera transmission in rural Bangladesh: Implications for vaccine and intervention targeting

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Abstract

We identify high risk clusters and measure their persistence in time and analyze spatial and population drivers of small area incidence over time. The geographically linked population and cholera surveillance data in Matlab, Bangladesh for a 10-year period were used. Individual level data were aggregated by local 250 × 250 m communities. A retrospective space-time scan statistic was applied to detect high risk clusters. Generalized estimating equations were used to identify risk factors for cholera. We identified 10 high risk clusters, the largest of which was in the southern part of the study area where a smaller river flows into a large river. There is persistence of local spatial patterns of cholera and the patterns are related to both the population composition and ongoing spatial diffusion from nearby areas over time. This information suggests that targeting interventions to high risk areas would help eliminate locally persistent endemic areas.

Keywords

Cholera; Vaccine; Matlab; Spatiotemporal cluster; Endemic area

1. Introduction

Cholera is a waterborne disease that has historically been endemic in several developing countries, especially in Bangladesh, India, some parts of Africa, and most recently in Haiti (WER, 2014). The epidemiological patterns of cholera depend largely on several environmental factors that include sanitary conditions, behaviours related to water, sanitation and hygiene, and prior immune status of the population at risk (Kanungo *et al*., 2012).

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Contributors

NN and MA contributed to the study design. MY contributed to the implementation and supervision of the study. NN and MA analyzed the data and took responsibility for the accuracy of the data analysis. All authors participated in the writing the manuscript and approved the final version of the manuscript.

Control efforts have traditionally focused on improving case management and increasing availability of safe drinking water (Azman *et al.*, 2015). Recently, a killed whole-cell oral cholera vaccine (OCV) has been used to control the disease, particularly for outbreaks, where quick action is needed (Luquero *et al.*, 2014). However, cholera has remained a serious public health concern in endemic countries despite our advanced knowledge about cholera epidemiology and the control mechanisms. Sadly, not much initiative has been taken so far for eliminating the threat of cholera in endemic countries. The reason is complex including not knowing when and where the interventions need to be implemented in the resource limited countries where cholera is endemic.

Since disease variation has a spatial expression, understanding the geographical distribution of disease is of considerable importance to public health workers and epidemiologists (Lawson, 2001). Importantly, identification of spatiotemporal clustering of cases, i.e., where and when the incidence is abnormally high, is important for public health officials to understand the nature of a disease and launch timely surveillance and intervention programs at the correct sites facilitating better allocation of resources (Kelsall et al., 2002). Cholera has been shown to be clustered within endemic areas (You et al 2013) and, once the high incidence areas are known, an effective intervention can be planned to stop the transmission at the source (called source drying), which would help prevent the spread of the disease to other areas. Implementing such a source drying program is important for eliminating the threat of cholera in endemic countries. With the increasing availability of the OCV and financial support from the Global Vaccine Alliance (Gavi), it is important to develop and implement an effective cholera control strategy in endemic countries to eliminate the threat of the disease.

In Matlab, a rural area of Bangladesh, cholera is known to be endemic. Thus, it is important for local public health officials to establish an intervention program that could turn the endemic area into a non-endemic area, using our knowledge of effectivecontrol strategies. The first step is to identify the source of transmission so that an effective control strategy can be planned. Previous geographic studies conducted on cholera were separated from the temporal ones (Ali *et al.*, 2002) or failed to delineate spatiotemporal risk clusters of cholera (Ruiz-Moreno et al, 2010), thus the source of transmission remained unknown. The primary objective of this study is to identify places with a greater density of cholera incidencein space and time, and perform an area-based analysis to determine the influence of specific environmental factors on cholera incidence. This knowledge will thus be used to develop strategies that will be part of an effective cholera control program.

2. Materials and methods

2.1. The Study Area

The study area, Matlab, is situated apprimately 55 kilometers southeast of Dhaka, the capital of Bangladesh, lies in the East-Central plain of the country, the delta formed by the Meghna and the Ganges rivers. The geographic positioning of the center of Matlab is 23°23’18.5”north latitude and 90°43’12.12” east latitude. The Dhonagoda River flows from north to south bisecting the study area into two approximately equal parts. Being flat and low-lying, the area is subjected to annual flooding. The houses are built on mounds of earth,

which raises them above the level of the normal monsoon floods. Use of tubewells for drinking water is common. Sanitary latrine use is low and the majority people use an open latrine. In the study area, the people live in clusters of patrilineally related households called *baris*. Each *bari* has an average of six households which include a total of about thirty people.

2.2. The data

The study was conducted within the icddr,b (International Centre for Diarrhoeal Disease Research, Bangladesh) Health and Demographic Surveillance System (HDSS) from 1991 to 2000. Initiated in 1966, the HDSS maintains records of all vital demographic events of the study area population (D'Souza, 1981). The people of the study area are identified by a unique identification (ID) number for all residents living in the HDSS system study area. To identify the household locations of the individuals, the HDSS maintains a *bari* ID, which is unique in the system. In 1994, a geographic information system (GIS) database was created for the study area to facilitate spatial analyses on health and population studies (Ali *et al.*, 2001). The GIS database includes *baris*, rivers, village boundaries, and health facilities. In this study population and spatial locational information were used from the HDSS.

The cholera data for the same period were obtained from the icddr,b's Matlab hospital surveillance system, which has in- and out-patient services as well as a laboratory for the identification of pathogens. We chose the data of that particular period because we believe it represents an endemic cholera setting; incidence was lower during post-2000 period.The Matlab hospital treats diarrhea cases at no cost to patients. Stool samples were collected from all patients who were residents of HDSS area. In case the patient has not passed stool or did not require admission rectal swabs were taken. As soon as specimen was collected, it was sent to the laboratory for screening enteric pathogens using standard culture method and determined their antimicrobial susceptibility. The hospital surveillance systems keep records of all the patients ever admitted in the hospital. The patients coming from the HDSS area are identified by their unique ID. The ID allows accessing demographic and socioeconomic conditions of the patients from the HDSS.

2.3. The spatial unit and data aggregation

Bari locations are represented as points in the study area geographic information system database. These points were aggregated into regions as the framework for this study in order to calculate incidence using a larger denominator than just the population of individual *baris*. Also grouping of the basic spatial units into larger units reduces the effect of suspected possible inaccuracies in the data (Ceccato *et al.*, 2002). To get the larger spatial units, we split the study area into grid cells of 250 × 250 m, which we call communities. The reason for selection of the specific size was based on the spatial process of cholera transmission that shows little transmission of the infections beyond 250 m (Debes *et al.*, 2016).

Individual-level data were aggregated by the communities. We counted only those people who were living in a *bari* on July 1 in each of the years included in the analysis. Distances to the Dhonagoda River and the Matlab hospital were calculated from the centroid of each community. Access to the health facility is important, because patients living in communities

farthest from the hospital are less likely to travel and seek care at the Matlab hospital. As sanitation is an important determinant, we calculated percentage of population using non-sanitary latrines in each mini-community by aggregating the number of households using non-sanitary latrines divided by the number of households living within the community multiplied by 100. Since cholera incidence was high among young children (<5 years of old), we also calculated percent of young children of the total population living in the community.

2.4. Space-time analysis

A retrospective space-time scan statistic was applied to detect high risk cluster(s) of cholera using SaTScan (version 9.1) with a discrete Poisson model. In the model, we used the number of cases and individuals for each community. Since SaTScan requires geographic coordinates for each observation, we used the centroids of the communities as the geographic reference points of the communities in the model. The space-time scan statistic is defined by a cylindrical window with a circular geographic base and with height corresponding to time (Kulldorff, 2011). The cylindrical window moves over space and time scanning for an elevated risk within the space-time window as compared to outside the window. The null hypothesis assumes that cholera cases are randomly distributed in space and time. The alternative hypothesis for each scanning window is that there is an elevated risk inside the window as compared to outside (Kulldorff, 1997). The difference of the incidence inside and outside each window was calculated by the log likelihood ratio (Chen *et al.*, 2008). Significant results were based on 999 Monte Carlo simulations.

We performed yearly scans using the data from 1991 to 2000 to observe changes in clustering and to control the time trend during the whole study period. As there was no consensus on optimal cluster size setting (Chen *et al.*, 2008; Tango and Takahashi, 2012), considering the size of the area and spatial distribution of population, we chose 20% of the population for the spatial window to allow the identification of small to medium-sized clusters. The height of the cylindrical window which reflects time was set to be 50% of the scan timeframe with a minimum of 2 years. To assess the stability of the spatial clusters over the follow-up period, we also carried out a purely spatial analysis for each two-year period.

2.5 Statistical analysis of the risk factors

We assessed the risk for cholera in a community using generalized estimating equations (GEE) with the logit link function and independent and exchangeable within-community correlation matrixes (Zeger *et al.*, 1998), considering that the panel data were correlated at the community level over time. The GEE took the occurrence of cholera in the community (yes/no) in each analyzed community as the dependent variable and the variables that showed significant association ($P<0.10$) with each of the outcomes in the bivariate model were selected for the final model. The independent variables included in the model were current year cholera incidence rate in the nearby communities/1000/year, past year cholera incidence in the community/1000/year, past year cholera incidence rate in the nearby communities/1000/year, distance from center of the community to the Matlab hospital (km), distance from the center of the community to the Dhonagoda Rover (km), percent of under five children in the community, and percent of households using non-sanitary latrine in the

community. Exponents of the coefficients of independent variables in the models were used to estimate the odds ratio (OR) of having cholera in a community. Standard errors for the coefficients were used to estimate p-values and associated 95% confidence intervals (95% CI) for the ORs. All statistical tests were interpreted in a two-tailed fashion. Analyses were performed using SAS Version 9.3.

2.6. Ethics

We used secondary data obtained from icddr,b under their data sharing policy. However, the original primary demographic and clinical data were collected after obtaining verbal informed consent from participants and legal guardians in case of minors.

3. Results

Splitting the study area into 250 × 250m of grid cell yielded 3,248 communities. We excluded grid cells that did not have any people during the study period (1991–2000) yielding 1,941 communities to be analyzed. For the assessment of risk factors, we excluded observations of 1991 due to inclusion of the past year cholera incidence rate in the communities resulting in 17,480 observations in the analysis. The characteristics of the study variables are shown in Table 1. The multivariable model shows increased risk for cholera in the communities was influenced by a higher proportion of under-five children living in the community and present and previous year cholera incidence rate in the nearby communities but not in the previous year cholera incidence in the community itself (Table 2). There was a decreased risk for cholera in a community further from the hospital (Table 2).

There were 4,776 cholera cases during the study period, of which 97% (4599/4746) were within 9 kilometers of the Matlab health facility. The number of cases varied by year (Figure 1). For the spatiotemporal model, we first evaluated magnitude of the effect of distance on cholera incidence using the data for the entire 10-year period. The results are shown in a line graph (Figure 2), which indicated that the cholera incidence rate started to drop after 6 kilometers from the health facility and ended up at a very low level (<0.50/1000) after 9 kilometers from the health facility. Since inclusion of population beyond 9 kilometers from the health facility would create artificial clusters of risk, we restricted our cluster analysis within 9 kilometers from the health facility, which provided 14,668 observations for the spatiotemporal model.

The spatiotemporal cluster model produced 10 high risk clusters of different sizes (Table 3). There was one large cluster in the southern part of the study area where the Dhonagoda River intersects with one of the large Meghna River (Figure 3). The cluster lasted for the entire study period (10 years) period and the risk was 66% higher in the cluster compared to outside of the cluster within the study area. Note that we did not map the clusters with size of 250m or less because they were too small to be considered a cluster. As cholera fluctuates each year, an analysis using the whole study period can only detect clusters in high incidence periods (Xie *et al.*, 2014). To observe the cluster change and control for the temporal trend in the entire study period, we conducted scanning in each two-year period and set maximum the population at risk to be 20% of the study area. The results of the purely spatial cluster analysis are shown in Figure 4. Again, most of the high risk clusters

were located in the southern part of the study area. These clusters either intersected with or were completely within the cluster areas identified through the space-time scan analysis (Table 4).

4. Discussion

This study explored the spatiotemporal clustering of cholera in an endemic area of Bangladesh using a 10-year daily time-series. Our findings suggest that cholera is spatially heterogeneous indicating not all communities are equally at risk of the disease. We identified a large cluster in the southern part of the area where the Dhonagoda River flows into the Meghna River, a major river of Bangladesh, and where cholera was found to be highly incident throughout the 10-year study period. We also observed two other small clusters alongside the smaller Dhonagoda River in some of the years studied. Clusters occurred in places farther away from the river could be treated as the secondary clusters, i.e., cholera could have been transmitted there from the primary sources. The results of our study also give a clear indication of temporal stability of the clusters, as we observed a good agreement of these clusters when analyzing the data by a two-year period.

The results of our multivariable model shows a community had an increased risk of the disease when nearby communities had higher rates of cholera the previous year. This suggests that cholera transmission is locally transmitted through a local diffusion process (Emch et al. 2017). However, if a community experienced increased risk in the previous year was no more at high risk for cholera suggesting that the risk could have been influenced by naturally infection driven immunity of the population (Ali et al., 2011). The positive relationship between the risk of cholera and the distance to the health facility can be attributed to healthcare seeking behavior of the community people in the rural area; the further the people live from a health facility the lower the number of patients who travel to the health facility from that community (Awoyemi et al., 2011). The risk for cholera in young children is higher in endemic countries compared to that among older individuals is well documented (Deen et al., 2008).

There are several limitations in this study. First, we have not tested the mechanism through which those specific areas influenced spatial clustering of cholera. However, the resulting map shows the largest and two other small clusters intersected with the river of the area illustrating the transmission may be related to the water source (Ruiz-Moreno et al 2010). Second, the results of the spatiotemporal scan statistic are sensitive to the parameter choices related to cluster scaling. Considering the size of study area and spatial distribution of the population, we chose 20% of the population at risk for the spatial window and 50% of the study period for the temporal widow with a minimum cluster duration to be 2 years. A choice higher than 20% of population at risk would detect a cluster containing some low risk areas leading to much larger than the true cluster size (Chen et al 2008). In contrast, significant clusters would be missed using a parameter that is less than 20% of the population of risk. Third, since the method uses a circular spatial scan it does not allow for irregular geographic shapes. Fourth, the modifiable areal unit problem resulting from the aggregation of the individual level data in to the defined communities (Wong, 2009; Eastwood et al., 2013). Although the communities defined based on the spatial scale of

cholera transmission in that setting, the results could be varied if we would have defined a different size of the community.

In conclusion, the results of our analysis indicates that there is persistence of the local spatial patterns of cholera and the patterns are related to both the population composition and the ongoing transmission from nearby areas. This information suggests that targeting interventions to areas with persistent endemic cholera and to children would help eliminate these locally persistent endemic areas.

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Highlights

- Cholera is endemic in Bangladesh
- A 10-year geocodedcholera surveillance dataset in rural Bangladeshwas used to charecterize local clusters in space and time
- Persistence of the local clustering is related to both the population composition and ongoing spatial diffusion from nearby areas over time
- The risk for cholera in a community was attributed to a higher proportion of under-five children living in the area and the cholera incidence rate in nearby communities in both the present and previous year
- Targeting interventions in communities that have persistent endemic cholera would be an effective strategy to eliminate cholera and block difussion of the disease

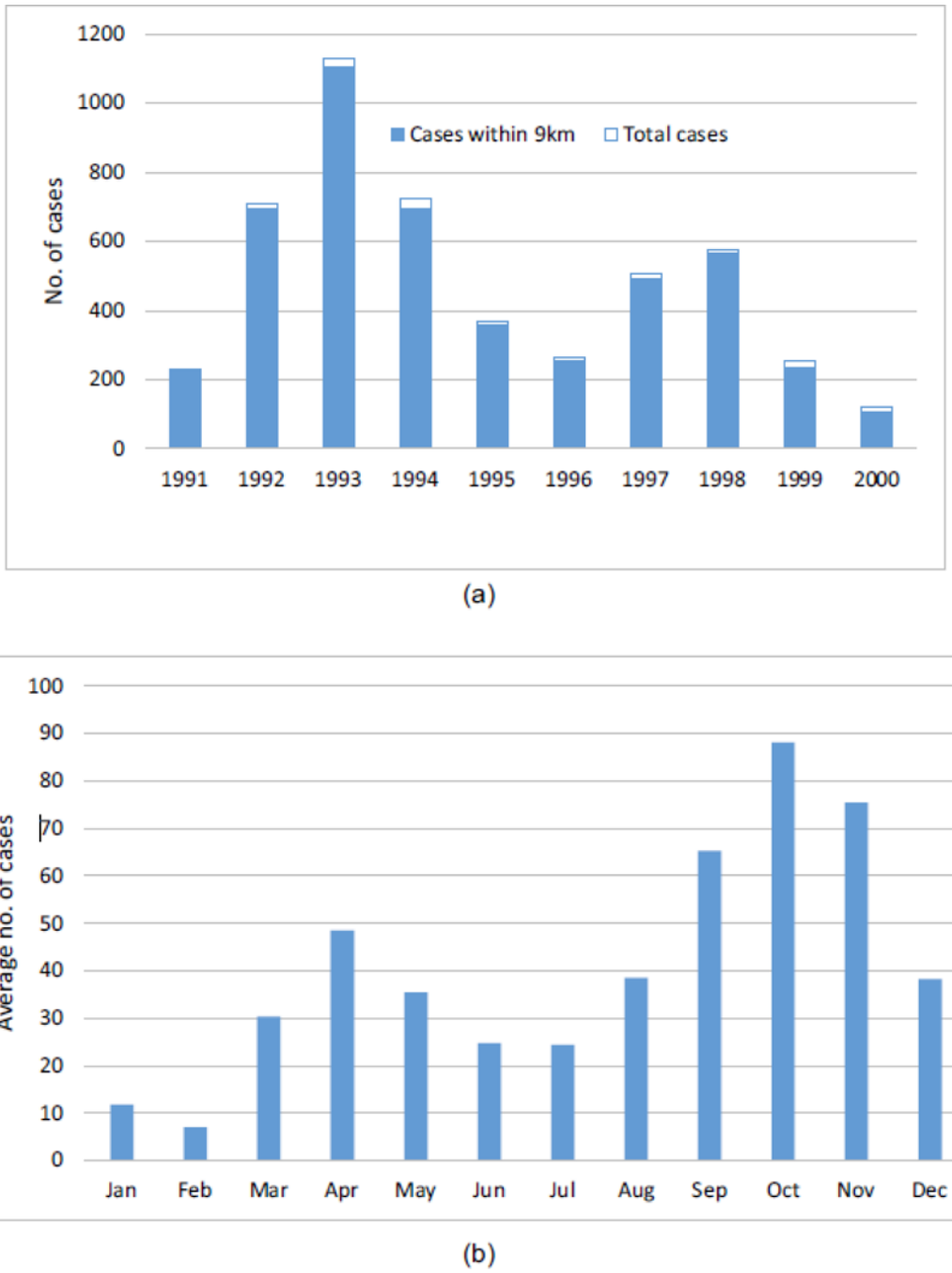

Figure 1.

(a) Number of cholera cases by year during the study period. (b) Average number of cholera cases (entire study area) by month during the study period

Figure 2.
Cholera incidence rate/1000 by distance to the hospital (kilometer) in Matlab, Bangladesh, 1991–2000

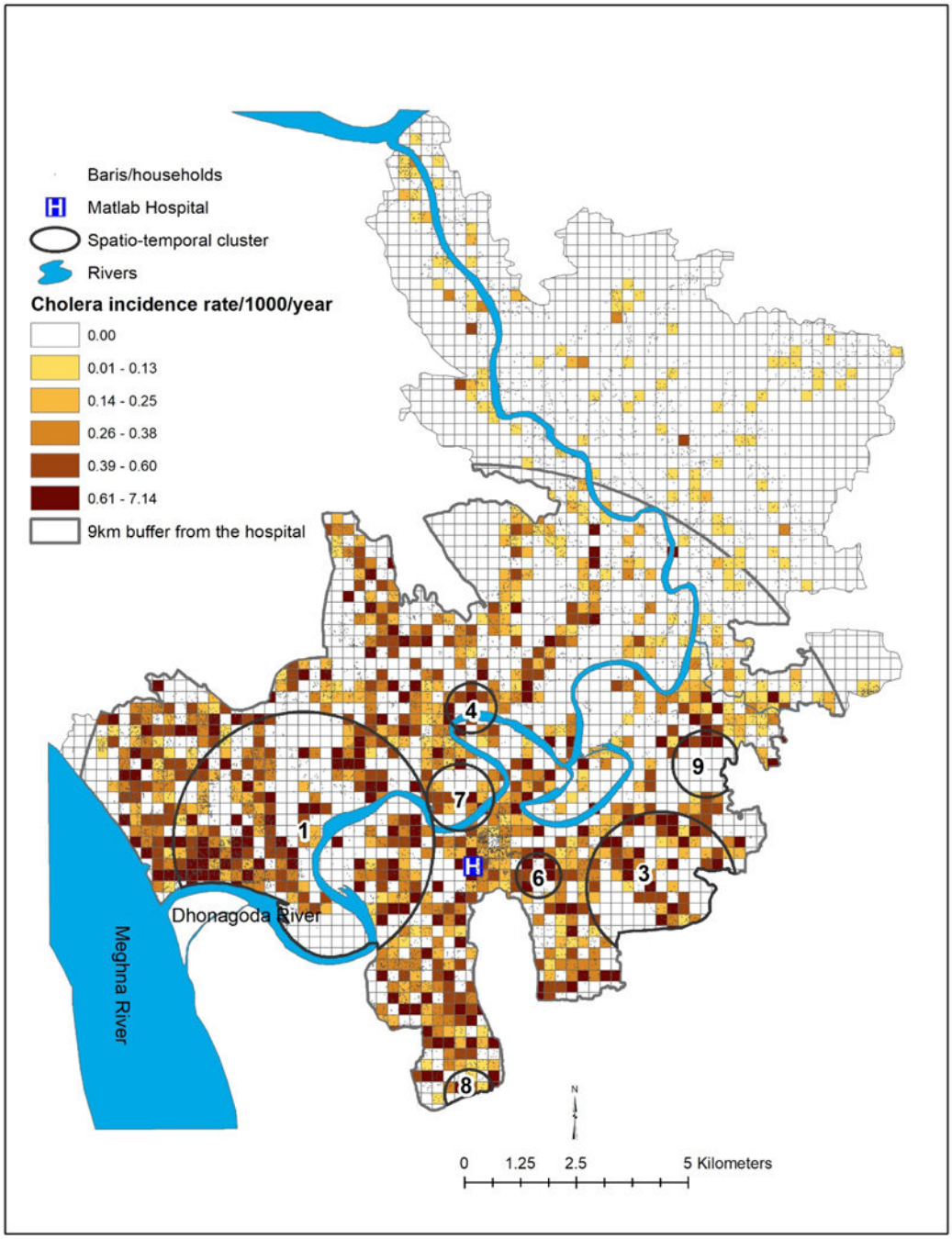

Figure 3.
Clusters of spatiotemporal risk for cholera in Matlab, Bangladesh, 1991–2000

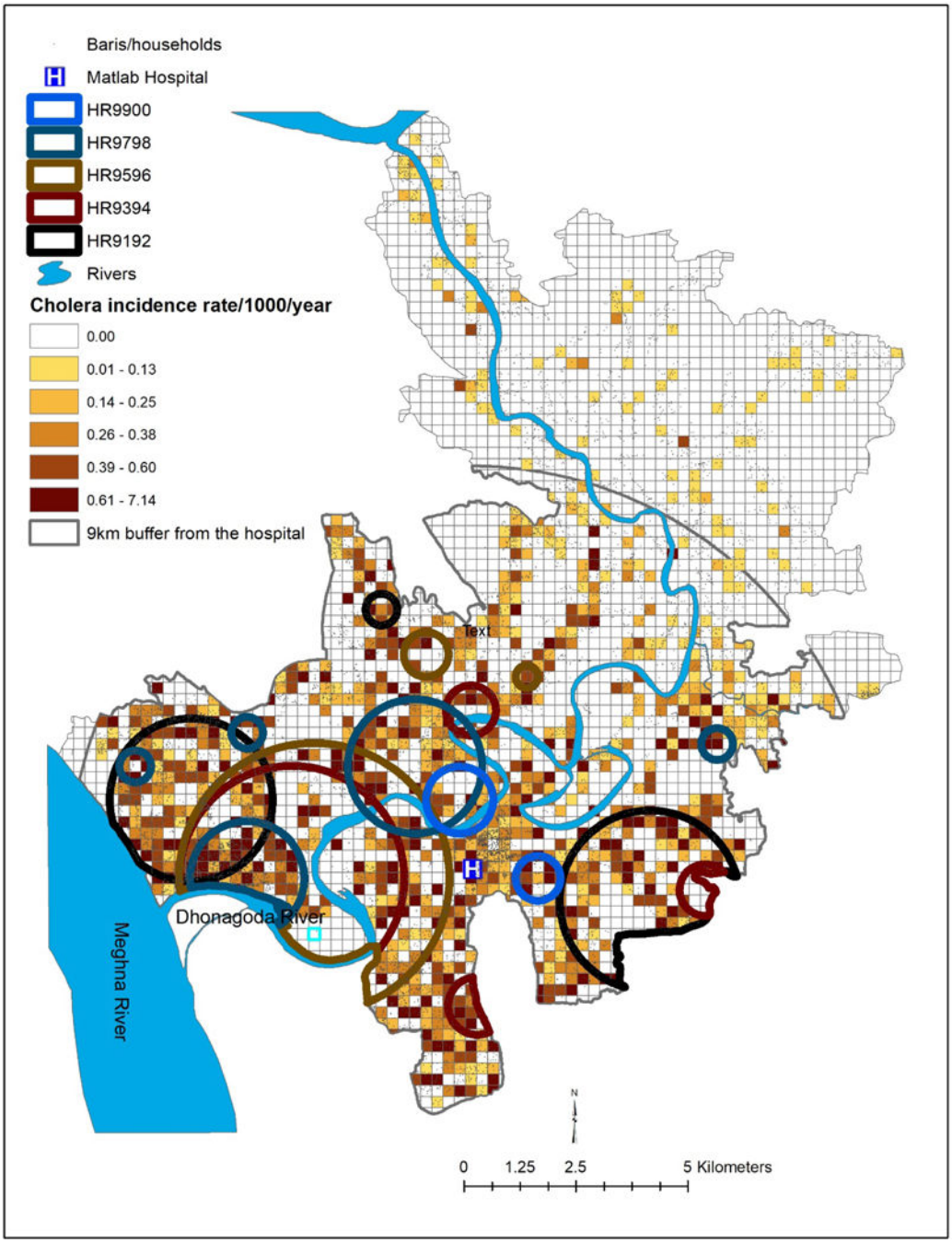

Figure 4.
Spatial clusters of higher risk for cholera in Matlab, Bangladesh by two-year period, 1991–2000

Table 1.

Characteristics of the study variables, Matlab, Bangladesh (n=17,480)

Variable	Mean	Std Dev	Minimum	Maximum
Current year cholera incidence rate in the nearby communities/1000/year	2.43	4.34	0.00	181.82
Past year cholera incidence in the community /1000/year	2.29	12.94	0.00	1000.00
Past year cholera incidence rate in the nearby communities/1000/year	2.52	4.37	0.00	181.82
Distance from center of the community to the Matlab hospital (km)	6.46	3.72	0.08	16.71
Distance from the center of the community to the Dhonagoda River (km)	1.25	1.21	0.00	6.16
Percent of under five children in the community	12.50	6.05	0.00	66.67
Percent of households using non-sanitary latrine in the community	81.55	23.81	0.00	100.00

Table 2.

Risk factors for cholera in Matlab, Bangladesh, 1991–2000

Variable	Odds ratio	95% CI	P-value
Current year cholera incidence rate in the nearby communities/1000/year	1.10	1.08–1.11	<.0001
Past year cholera incidence in the community /1000	1.00	0.99–1.01	0.1506
Past year cholera incidence rate in the nearby communities/1000/year	1.03	1.02–1.04	<.0001
Distance from center of the community to the Matlab hospital (km)	0.87	0.84–0.89	<.0001
Distance from the center of the community to the Dhonagoda River (km)	0.98	0.91–1.04	0.4817
Percent of under five children in the community	1.02	1.01–1.03	<.0001
Percent of households using non-sanitary latrine in the community	1.00	0.99–1.00	0.2587

Table 3.

Cholera incidence analysis using space-time scan statistic

Cluster No.	x	y	Size of the cluster*	Risk period	No. observed cases	No. expected cases	Relative risk**	Log-likelihood ratio	P-value
1	568465.5185	581781.2153	2915	1991–2000	1312	890	1.66	112.11	0.001
2	570215.5185	587031.2153	250	1992–1993	43	10	4.21	28.88	0.001
3	576465.5185	580781.2153	1677	1991–1992	112	50	2.26	28.44	0.001
4	572215.5185	584781.2153	559	1993–1997	65	22	3.01	28.07	0.001
5	566465.5185	584281.2153	250	1992–1993	40	9	4.28	27.43	0.001
6	573715.5185	581031.2153	500	1999–2000	16	2	6.76	16.92	0.003
7	571965.5185	582781.2153	750	1998–2000	30	9	3.25	14.52	0.022
8	572174.9299	576128.6423	556	1994–1996	26	8	3.46	13.75	0.037
9	577465.5185	583531.2153	750	1998–1999	15	3	5.53	13.34	0.043
10	574715.5185	586781.2153	250	1994–1995	15	3	5.53	13.34	0.043

*radius in meter from the x and y coordinates

**The estimated risk within the cluster divided by the estimated risk outside the cluster. The estimated risk was calculated as the observed divided by the expected number of cases.

Table 4.

Percent of clusters from purely spatial analysis overlapped/intersected with the clusters from spatiotemporal analysis

Year of analysis	No. of clusters	No. of clusters overlapped/intersected *	Percent of clusters overlapped/intersected *
1991–1992	3	2	66.7
1993–1994	3	2	66.7
1995–1996	3	1	33.3
1997–1998	5	4	80.0
1999–2000	2	2	0.0

* Overlapped/intersected with spatiotemporal clusters