Geographically Weighted Regression Modeling of Spatial Clustering and Determinants of Focal Typhoid Fever Incidence

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Background. Typhoid is known to be heterogeneous in time and space, with documented spatiotemporal clustering and hotspots associated with environmental factors. This analysis evaluated spatial clustering of typhoid and modeled incidence rates of typhoid from active surveillance at 4 sites with child cohorts in India.

Methods. Among approximately 24,000 children aged 0.5–15 years followed for 2 years, typhoid was confirmed by blood culture in all children with fever >3 days. Local hotspots for incident typhoid cases were assessed using SaTScan spatial cluster detection. Incidence of typhoid was modeled with sociodemographic and water, sanitation, and hygiene–related factors in smaller grids using nonspatial and spatial regression analyses.

Results. Hotspot households for typhoid were identified at Vellore and Kolkata. There were 4 significant SaTScan clusters (P < .05) for typhoid in Vellore. Mean incidence of typhoid was 0.004 per child-year with the highest incidence (0.526 per child-year) in Kolkata. Unsafe water and poor sanitation were positively associated with typhoid in Kolkata and Delhi, whereas drinking untreated water was significantly associated in Vellore (P = .0342) and Delhi (P = .0188).

Conclusions. Despite decades of efforts to improve water and sanitation by the Indian government, environmental factors continue to influence the incidence of typhoid. Hence, administration of the conjugate vaccine may be essential even as efforts to improve water and sanitation continue.

Keywords. typhoid incidence; hotspots; SaTScan clusters; spatial autocorrelation; geographically weighted regression.

Typhoid fever, caused by Salmonella enterica serovar Typhi, is an important public health problem leading to substantial morbidity and mortality. The disease burden varies between and within countries. The World Health Organization estimates that worldwide around 11–20 million people acquire the disease and >150,000 people die annually [1–3].

In India, a recent systematic review estimated prevalence of typhoid fever from various hospital-based studies at 7% (95% confidence interval [CI], 5.7%–16.0%) and was higher during local disease outbreaks. Information regarding the burden of typhoid fever in community settings from India was limited. The pooled incidence of laboratory-confirmed typhoid fever across all studies was 377 (95% CI, 178–801) per 100,000 person-years and highest among children aged 2–4 years, with significant heterogeneity between different studies [4].

Several epidemiological studies have identified either water or foodborne routes as the primary mechanisms involved in transmission of typhoid fever. The disease is higher in population that lack access to safe water and adequate sanitation. Economically poorer communities and vulnerable population subgroups, including children, are at highest risk. Household-level characteristics including larger household size, recent typhoid fever in the household, members not using soap for hand washing, sharing food, and absence of a toilet are documented independent risk factors for typhoid fever [2, 5–7].

Geographic information science has been used to study at-risk areas and spatial clustering of typhoid fever. Typhoid, as with other diarrheal diseases, often exhibits geographic patterns due to its feco-oral mode of transmission, mainly through shared water supplies. Spatial and temporal clustering of typhoid cases has been documented at subnational levels [8–11], with local hotspots within smaller geographic regions associated with environmental factors [12–14]. Studies on typhoid examining spatial patterns and relationships at still finer scale of local neighborhoods and living environments are limited.
The multicentric Surveillance for Enteric Fever in India (SEFI) study was conducted to obtain reliable and high dimensional estimates of burden of typhoid fever using multiple strategies in both urban and rural settings across the country [15]. This paper mapped and evaluated spatial clustering of typhoid fever; detected hotspots; and modeled incidence rates of typhoid fever, evaluating relationships with family-level sociodemographic and water, sanitation, and hygiene (WASH) practices in the 4 cohorts of the SEFI study.

**METHODS**

**Data Sources and Spatial Mapping**

The multicentric SEFI study was initiated in October 2017 with the objectives of (1) estimating the incidence of typhoid fever in children between 6 months and 15 years of age across 4 sites—3 urban (Vellore, Kolkata, and Delhi) and 1 rural (in Pune)—though an active community-based cohort surveillance (tier 1); (2) estimating the incidence of severe typhoid fever in all ages using a hybrid approach combining hospitalization and healthcare utilization data; (3) monitoring patterns of antimicrobial use and antimicrobial resistance in patients with typhoid fever; and (4) estimating cost and consequences of typhoid fever in different healthcare settings (tiers 2 and 3) in India [15].

The detailed study protocol, including sample size calculations, has been published previously [15], and the study was registered with the Clinical Trial Registry of India (CTRI/2017/09/009719). Sociodemographic and geospatial data and information on occurrence of blood culture–confirmed typhoid fevers among the study participants were obtained from the active surveillance (tier 1) component of the SEFI study. Geocoordinates of residences of consenting study families were collected during enrollment and subsequent home visits during follow-up of acute febrile illnesses in the community using electronic survey instruments. Spatial mapping of the boundaries of the study area was performed by trained field research assistants using handheld global positioning devices. Study area polygons and study houses were mapped, and spatial analyses were performed using ArcGIS Desktop 10.7.1 software [16].

**SPATIAL ANALYSIS**

**Spatial Clustering and Hotspot Analyses**

Local hotspots for incident cases of typhoid fever were assessed using the Optimized Hot Spot Analysis by Getis-Ord G* local statistic tool in ArcGIS 10.7 to detect statistically significant spatial clusters of high values (hotspots) and low values (coldspots) across the 4 study sites. The statistic returns a z score for each feature in the dataset; the larger the z score, the more intense the clustering of high values (hotspots) [17–22].

SaTScan software version 9.7, developed by Kulldorff, was used to detect and evaluate spatial clusters of typhoid fever at the sites using a purely spatial Poisson-based scanning model running a circular scanning window. SaTScan scans across time and/or space were used to identify possible clusters by comparing the number of observed events and expected events inside the window at each location. Clusters with significant levels with cutoff values such as .05, .01, and .001 after repeated Monte Carlo simulations were reported. The cluster with the maximum log likelihood ratio was taken as the most likely cluster (least likely to be due to chance). Secondary clusters in the regions were also identified, and only nonoverlapping significant spatial clusters with high rates are presented [11, 23–28].

**Incidence of Typhoid Fever and Spatial Autocorrelation Analysis**

Since the rural cohort in Vadu, Pune had sparse cases of typhoid fever during the entire study duration, this site was excluded from further spatial analyses.

Polygon feature classes of tessellated regular hexagonal grids were created for each of the study sites with an approximately 2500 m² area (50 m × 50 m) using geoprocessing tools in ArcGIS 10.7 [29, 30]. Incident cases of typhoid were aggregated for these grids and incidence rates for the study duration were estimated for the grids. The zero inflated incidence data was normalized using the double arcsine Freeman–Tukey transformation technique [31–33]. The formula for the Freeman–Tukey double-arcsine transformation was

\[
f(r, n) = \arcsin \left( \sqrt{\frac{r}{n + 1}} \right) + \arcsin \left( \sqrt{\frac{r + 1}{n + 1}} \right)
\]

where \( r = \text{number of events} \) and \( n = \text{person-time of follow-up} \).

To assess the degree of clustering and spatial patterns at each of the 3 sites (Vellore, Kolkata, and Delhi), local spatial autocorrelation was assessed using local indicators of spatial association, estimated using the Anselin local Moran I statistic for transformed typhoid incidence rates (per child-year [CY]) in the hexagonal grids using the Cluster and Outlier analysis tool in ArcGIS 10.7. A positive value for the statistic I indicated that a grid had neighboring grids with similar high or low incidence rates and was a part of a cluster. A negative value for I indicated that the grid had neighbors with dissimilar values. Spatial autocorrelation classified the features into “hotspots” (high values surrounded by high [HH]) or “coldspots” (low values next to low [LL]) and outlier clusters such as HL (high among low neighbors) or LL (low among low neighbors); those grids with \( P \) values <.05 were considered statistically significant [21, 34–38].

**Spatial Regression Analysis**

To better understand the influence of sociodemographic and WASH-related factors behind observed disease incidence rates in the local tessellated grids, initially, a global regression method—the ordinary least squares regression (OLS) analysis [39, 40]—was performed individually across 3 sites (Vellore, Kolkata, and Delhi) using the spatial statistics tools in ArcGIS...
cases were recorded from all 4 sites for the years 2018 and the last quarter of 2017 from Vellore. A total of 91 and 176 Of the 299 typhoid cases, 30 (10%) were documented during Spatiotemporal Distribution of Typhoid Fevers

RESULTS

A total of 24 062 children were enrolled across 4 sites, with 24 470 (89.2%) completing 24 months of follow-up. Of the 4 sites, Vellore, Kolkata, and Delhi represented urban communities with geographic areas of 2.20, 4.15, and 0.42 km², respectively, while the site in Vadu, Pune with an area of 79 km² represented the only rural community in the tier 1 component of the SEFI study. During the study period, 299 incident cases of blood culture–confirmed typhoid fever were documented across the 4 sites; the highest number of cases was 146 from Vellore and there were only 4 cases from Vadu, Pune. Cases of typhoid fever were distributed across the study sites except in Vadu, where all 4 cases were observed in 1 locality (Figure 1).

Spatiotemporal Distribution of Typhoid Fevers

Of the 299 typhoid cases, 30 (10%) were documented during the last quarter of 2017 from Vellore. A total of 91 and 176 cases were recorded from all 4 sites for the years 2018 and 2019, respectively. Cases of typhoid occurred in almost all months in Vellore and Kolkata. In Vellore, peak cases (56%) occurred during the second quarter (April to June) of 2018 and 2019, while 72% (58/81) and 64% (42/66) of cases were in the last 2 quarters in Kolkata and Delhi, respectively. Cases were densely distributed across 2 geographical localities in Vellore and Kolkata during the peak seasons, but no specific spatial pattern was seen in the denser Delhi cohort. Seasonality of incident typhoid cases and their spatial distribution are presented in Figure 2 and Supplementary Figures 1 and 2.

Spatial Clustering and Hotspots of Typhoid Fever

Aggregating spatial data on incident cases of typhoid fevers and correcting for both multiple testing and spatial dependence, a total of 856 cohort households were identified as significant hotspots for typhoid at the 4 sites using the optimized Getis-Ord Gi* statistic. Vellore with 146 typhoid cases had 365 hotspot cohort households whereas Kolkata, Delhi, and Pune had 131, 175, and 186 households identified as potential hotspots during the study period (Figure 3).

Focal Incidence of Typhoid Fever in the Study Cohorts

There were 2421 hexagonal grids with at least 1 study household across the 4 study sites. The mean numbers of people and children aged <15 years per grid were 30.1 (standard deviation [SD], 0.4) and 11.7 (SD, 16.9) respectively. Mean incidence of typhoid fever in the grids was 0.004 (SD, 0.022) per CY and the highest incidence was 0.526 per CY. The Vellore and Kolkata sites had a few pockets with incidence rates >0.15 per CY (Figure 4).

Local Spatial Autocorrelation Analysis

Of the 1503 tessellated grids with study households across Vellore, Kolkata, and Delhi, 132 (8.7%) were high-high (HH) clusters for typhoid fever. Vellore had 11.4% (80/704) HH clusters concentrated in 2 local neighborhoods toward the middle and south of the study area. In Kolkata, the HH clusters (48/624 [7.7%]) were located toward the western part of the study area; the Delhi site, with only 2.3% of grids being HH clusters, did not demonstrate any geographic pattern (Figure 5).

Sociodemographic Predictors of Typhoid Fever Incidence

Exploratory regression analysis using the multivariate OLS regression model incidence of typhoid and its relationship to collected family-level sociodemographic and WASH practices
Figure 1. Location of the 4 cohort sites in the Surveillance for Enteric Fever in India (SEFI) study. The 3 urban sites included Vellore, Kolkata, and Delhi. The only rural site was in Vadu, Pune.
Figure 2. Seasonality in occurrence of typhoid cases across the 4 Surveillance for Enteric Fever in India (SEFI) cohort sites. This graph presents the occurrence of incident typhoid cases during different months across the 4 cohorts. Enrollment in Vellore started in late 2017, whereas the other sites started in 2018.

Figure 3. Spatial hotspots and clustering of typhoid cases in the Surveillance for Enteric Fever in India (SEFI) study cohorts. Hotspot households for typhoid were present in all 4 sites, whereas significant SaTScan clustering was detected only in Vellore.
at the grid level revealed that not all variables were consistently associated with burden of typhoid across the 3 locations. The number of study families in the grids consistently showed a significantly negative association across all 3 locations, while the proportion of overcrowded families was positively associated with disease incidence in the Delhi site. Unsafe water and poor sanitation were positively associated, although not statistically significant, in Kolkata and Delhi. The proportion of families

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**Figure 4.** Focal incidence of typhoid fever across 3 Surveillance for Enteric Fever in India cohort study locations. Local neighborhoods with high typhoid incidence rates were present in Vellore and Kolkata and appeared to be randomly distributed.

**Figure 5.** Spatial patterns and clustering of typhoid disease in neighborhoods across 3 Surveillance for Enteric Fever in India study cohort sites. High-high clusters for typhoid disease incidence were detected in Vellore and Kolkata and demonstrated specific spatial patterns.
drinking untreated drinking water was significantly associated with typhoid incidence in both the Vellore \((P = .034)\) and Delhi \((P = .018)\) cohorts whereas in Kolkata, a nonsignificant positive association was detected. The proportion of families buying ready-to-use cooked food from local vendors associated with typhoid, was significantly higher in Kolkata \((P = .018)\) cohorts whereas in Delhi, a nonsignificant positive association was detected. The proportion of families buying ready-to-use food from local shops were \(0.0121 (P = .51)\), \(0.0161 (P = .28)\), and \(-0.0676 (P = .26)\) respectively.

### DISCUSSION

The 4 locations included in the study varied in terms of catchment area, with the urban area in Delhi spanning 0.42 km² and the only rural site in Pune distributed over 79 km². Typhoid disease incidence rates varied across the sites: lowest in the rural location \((35 per 100 000 CY)\) and the highest in periurban communities of Vellore \((1173 per 100 000 CY)\) (John et al, unpublished data), indicating wide heterogeneity in disease burden among children in the study cohorts.

In Vellore, typhoid cases were documented consistently during the study period except during the months of May–July in the year 2019 when the highest number of cases occurred coinciding with the relaying of a sewage network in these urban neighborhoods as part of the Smart City campaign, which could have resulted in a local outbreak of typhoid fever. In Kolkata and Delhi, higher numbers of cases were seen during the last 2 quarters, which normally are the monsoon and postmonsoon seasons. During the peaks, cases of typhoid were spatially located in certain localities of the study areas in Vellore and Kolkata, indicating limited geographic spread in these cohorts. In Pune, of the 4 cases, 2 were in the same locality but during different time points.

In Vellore, houses within close proximity (within a radius of 150 m) of a typhoid case were at significantly higher risk of typhoid, indicating pockets of focal transmission around the case houses, likely due to environmental exposure to contaminated drinking untreated drinking water and standard residuals of the OLS across 3 cohorts (Table 1).

### Table 1. Multivariate Ordinary Least Squares Regression and Geographic Weighted Regression Models Using Transformed Incidence of Typhoid Fever at the Vellore, Kolkata, and Delhi Sites of the Surveillance for Enteric Fever in India Study

| Variable | Vellore | Kolkata | Delhi |
|----------|---------|---------|-------|
| Intercept | \(0.29752\) | \(0.039275\) | \(0.080425\) |
| No. of Study Families in the Grid | \(-0.00046\) | \(-0.00064\) | \(-0.00077\) |
| Proportion of Families Belonging to Lower Socioeconomic Status | \(-0.01989\) | \(-0.01277\) | \(-0.01441\) |
| Proportion of Overcrowded Families | \(-0.01303\) | \(-0.0019\) | \(0.03664\) |
| Proportion of Families with Access to Unsafe Water | \(-0.033016\) | \(0.023812\) | \(0.073252\) |
| Proportion of Families Not Treating Drinking Water Before Use | \(0.036626\) | \(0.013631\) | \(0.08121\) |
| Proportion of Families with Unsafe Sanitation | \(-0.019394\) | \(0.026532\) | \(0.020172\) |
| Proportion of Families Buying Ready-to-Use Food from Local Shops | \(-0.011993\) | \(0.081287\) | \(0.039254\) |
| Proportion of Families with Children Consuming Locally Sold Ice Candy | \(0.034116\) | \(0.033133\) | \(0.044577\) |
| Adjusted \(R^2\) | 0.2667 | 0.2835 | 0.2667 |
| Adjusted \(R^2\) (GWR) | 0.226 | 0.226 | 0.226 |

**Abbreviations:** AICc, corrected Akaike information criterion; GWR, geographic weighted regression; OLS, ordinary least squares; SE, standard error.

*\(P < .05\) is considered statistically significant.

The proportion of families consuming untreated water in the hexagonal grids was a strong predictor in the northern and southeastern parts of the Vellore catchment area, whereas it was more in the centrally distributed families in Kolkata and in the western neighborhood in the Delhi catchment area (Figure 6A). Mapping of standard residuals of the GWR revealed absence of overestimation (blue grids) and a random distribution of underestimation (red grids) of typhoid incidence across the 3 regions as indicated by the Moran indices for standard residuals (Figure 6B). Moran \(I\) values for Vellore, Kolkata, and Delhi were \(0.0121 (P = .51)\), \(0.0161 (P = .28)\), and \(-0.0676 (P = .26)\) respectively.

The proportion of families consuming untreated water and standard residuals of the GWR across 3 regions as indicated by the Moran indices for standard residuals (Figure 6B). Moran \(I\) values for Vellore, Kolkata, and Delhi were \(0.0121 (P = .51)\), \(0.0161 (P = .28)\), and \(-0.0676 (P = .26)\) respectively.
water or food. Although similar hotspot households were detected in the Kolkata study site, there was no significant spatial clustering of cases. Since spatiotemporal analyses was not performed, we could not assess whether these hotspots or clusters varied with both time and space at the study sites.

Since incident typhoid cases demonstrated specific spatial patterns in these cohorts, disease burden and relationship with predictors were assessed at grid level. Three pockets with highest typhoid incidence (>0.25 per CY) were detected at the Kolkata site while 1 pocket each in Vellore and Delhi had incidence rates of 0.21 and 0.08 per CY, respectively. The locations of significant clusters with higher typhoid incidence (HH clusters) did not spatially overlap with the clusters of typhoid cases as anticipated since incidence was estimated for all the households within the grid at grid level and is a function of person-time of follow-up.

Studies have documented that in addition to sociodemographic factors and WASH-related behaviors, typhoid occurrence is influenced by neighboring regions [7, 14, 48–50].

Figure 6. Mapping coefficients (A) and standard residuals (B) of the geographically weighted regression analysis. Coefficients for proportion of families consuming untreated water exhibited distinct spatial patterns, and there was no overestimation with a randomly distributed underestimation of typhoid incidence in the grids. Abbreviations: GWR, geographically weighted regression; SD, standard deviation.

Modeling grid level–transformed typhoid incidence with sociodemographic and WASH predictors in this analysis by OLS regression found a negative relationship between number of study families and disease burden at the grid level, which was contrary to expectations. Similarly, we did not detect a positive relationship between proportion of lower socioeconomic status families and disease in both Vellore and Kolkata whereas in Delhi, a nonsignificant positive relationship was seen. Higher population densities and a homogenous distribution of families with similar sociodemographic characteristics across these urban settings may have influenced our findings. The proportion of families that did not practice point-of-use water disinfection was strongly associated with disease burden in the microenvironments studied. These findings suggest that the prevalent community-level water treatment practices were inadequate and do not offer sufficient protection against gastrointestinal diseases. At one of the sites, the practice of purchasing ready-to-use foods by the families was positively associated with typhoid, highlighting the importance of better
food hygiene and WASH practices, not only in the families but also in the neighborhoods.

Spatial modeling using the GWR adjusting for immediate neighborhoods and spatial nonstationarity confirmed that there was no overestimation of disease burden at the local grids and any underestimation was a random process in addition to strengthening the findings from the nonspatial regression analysis. Not accounting for meteorological predictors of typhoid disease is one of the limitations in this study.

**CONCLUSIONS**

The burden of typhoid disease was heterogeneous between urban and rural cohorts in the SEFI study. Local spatial clusters and hotspots among households were present within the urban cohorts. Within each urban cohort, marked variations were noted in the disease incidence rates at local neighborhood resolutions; presence of cases of typhoid in close proximities rendered the group of neighboring households at higher risk of acquiring the disease. Distribution of typhoid risk factors was uneven across the study cohorts. Not practicing point-of-use water treatment and consuming ready-to-use food available in the neighborhoods were significantly associated with disease burden. Despite decades of efforts to improve water and sanitation by the Indian government, environmental factors continue to influence the incidence of typhoid. Hence, administration of the conjugate vaccine may be essential even as efforts to improve water and sanitation continue.

**Supplementary Data**

Supplementary materials are available at *The Journal of Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

**Supplementary Figure 1.** Spatial distribution of incident typhoid cases for the year 2018. In the year 2018, higher numbers of typhoid cases were noted in the second quarter in Vellore and in the second and third quarters in Kolkata.

**Supplementary Figure 2.** Spatial distribution of incident typhoid cases for the year 2019. In the year 2019, higher numbers of typhoid cases were noted in the second quarter in Vellore and in the third and fourth quarters in the Kolkata and Delhi cohorts.

**Notes**

**Author contributions.** J. J. and G. K. conceived and designed the study. V. R. M., J. J., G. K., A. B., T. R. C., S. K., B. S., K. N. S., A. S., A. S. K., S. D., and K. R. developed the study protocol and analysis plan. M. S., K. N. S., A. B., A. S., T. R. C., B. S., S. K., S. D., S. K. N., S. K. G., A. G., and A. A. coordinated data collection at the sites. V. R. M., K. R., and S. K. G. analyzed the data. M. S. and V. R. drafted the manuscript. All authors have reviewed the manuscript and approved it. V. R. M., J. J., and G. K. had complete access to data and guarantee the manuscript.

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**References**

1. Wain J, Hendriksen RS, Mikoleit ML, Keddy KH, Ochiai RL. Typhoid fever. *Lancet* 2015; 385:1136–45.
2. World Health Organization. Typhoid. [https://www.who.int/news-room/fact-sheets/detail/typhoid](https://www.who.int/news-room/fact-sheets/detail/typhoid). Accessed 20 January 2021.
3. Marchello CS, Hong CY, Crump JA. Global typhoid fever incidence: a systematic review and meta-analysis. *Clin Infect Dis* 2019; 68:105–16.
4. John J, Van Aart CJC, Grassly NC. The burden of typhoid and paratyphoid in India: systematic review and meta-analysis. *PLoS Negl Trop Dis* 2016; 10:e0004616.
5. Black RE, Cisneros L, Levine MM, Banfi A, Lobos H, Rodriguez H. Case-control study to identify risk factors for paediatric endemic typhoid fever in Santiago, Chile. *Bull World Health Organ* 1985; 63:899–904.
6. Luby SP, Faizan MK, Fisher-Hoch SP, et al. Risk factors for typhoid fever in an endemic setting, Karachi, Pakistan. *Epidemiol Infect* 1998; 120:129–38.
7. Vollaard AM, Ali S, van Asten HA, et al. Risk factors for typhoid and paratyphoid fever in Jakarta, Indonesia. JAMA 2004; 291:2607–15.
8. Gatrell AC, Bailey TC. Interactive spatial data analysis in medical geography. Soc Sci Med 1996; 42:843–55.
9. Sur D, Ali M, von Seidlein L, et al. Comparisons of predictors for typhoid and paratyphoid fever in Kolkata, India. BMC Public Health 2007; 7:289.
10. Hinman SE, Blackburn JK, Curtis A. Spatial and temporal structure of typhoid outbreaks in Washington, D.C., 1906-1909: evaluating local clustering with the Gi* statistic. Int J Health Geogr 2006; 5:13.
11. Wang LX, Yang B, Yan MY, et al. Spatial and temporal clustering characteristics of typhoid and paratyphoid fever and its change pattern in 3 provinces in southwestern China, 2001-2012 [in Chinese]. Zhonghua Liu Xing Bing Xue Za Zhi 2017; 38:1504–8.
12. Ali E, Bergh RVD, D'hondt R, et al. Localised transmission hotspots of a typhoid fever outbreak in the Democratic Republic of Congo. Pan Afr Med J 2017; 28:179.
13. Dewan AM, Corner R, Hashizume M, Onge ET. Typhoid fever and its association with environmental factors in the Dhaka metropolitan area of Bangladesh: a spatial and time-series approach. PLoS Negl Trop Dis 2013; 7:e1998.
14. Corner RJ, Dewan AM, Hashizume M. Modelling typhoid risk in Dhaka metropolitan area of Bangladesh: the role of socio-economic and environmental factors. Int J Health Geogr 2013; 12:13.
15. John J, Bavadkar A, Rongsen-Chandola T, Dutta S, Kang G; NSSEFI Collaborators. Estimating the incidence of enteric fever in children in India: a multi-site, active fever surveillance of pediatric cohorts. BMC Public Health 2018; 18:594.
16. Esri. ArcGIS Desktop: release 10. 7. Redlands, CA: Esri, 2019.
17. Getis A, Ord K. The analysis of spatial association by use of distance statistics. In: Geographical analysis. Berlin: Springer, 1992:189–206.
18. Anselin L. Local indicators of spatial association—LISA. Geogr Anal 1995; 27:93–115.
19. Anselin L, Getis A. Spatial statistical analysis and geographic information systems. Ann Reg Sci 1992; 26:19–33.
20. Esri. ArcMap—optimized hotspot analysis (spatial statistics). https://desktop.arcgis.com/en/arcmap/latest/tools/spatial-statistics-toolbox/optimized-hot-spot-analysis.htm. Accessed 9 January 2021.
21. Wangdi K, Clements ACA, Du T, Nery SV. Spatial and temporal patterns of dengue infections in Timor-Leste, 2005–2013. Parasit Vectors 2018; 11:9.
22. Saxena R, Nagpal BN, Das MK, et al. A spatial statistical approach to analyze malaria situation at micro level for priority control in Ranchi district, Jharkhand. Indian J Med Res 2012; 136:776–82.
23. Kulldorff M. A spatial scan statistic. Commun Stat Theory Methods 1997; 26:1481–96.
24. Kulldorff M. SaTScan: user guide for version 9.7. https://www.satscan.org/cgi-bin/satscan/register.pl?SaTScan_Users_Guide.pdf?todo=process_userguide_download. Accessed 15 January 2021.
25. Acharya BK, Cao C, Lakes T, Chen W, Naeem S. Spatiotemporal analysis of dengue fever in Nepal from 2010 to 2014. BMC Public Health 2016;16:849.
26. Raghava MV, Prabhakaran V, Jayaraman T, et al. Detecting spatial clusters of Taenia solium infections in a rural block in South India. Trans R Soc Trop Med Hyg 2010; 104:601–12.
27. Pham Thanh D, Thompson CN, Rabaa MA, et al. The molecular and spatial epidemiology of typhoid fever in rural Cambodia. PLoS Negl Trop Dis 2016; 10:e0004785.
28. Odoi A, Martin SW, Michel P, Middleton D, Holt J, Wilson J. Investigation of clusters of giardiasis using GIS and a spatial scan statistic. Int J Health Geogr 2004; 3:11.
29. Esri. Generate tessellation (data management)—ArcGIS Pro. Documentation. https://pro.arcgis.com/en/pro-app/latest/tool-reference/data-management/generatetesellation.htm. Accessed 19 January 2021.
30. Birch CPD, Oom SP, Beecham JA. Rectangular and hexagonal grids used for observation, experiment and simulation in ecology. Ecol Model 2007; 206:347–59.
31. Freeman MF, Tukey JW. Transformations related to the angular and the square root. Ann Math Stat 1950; 21:607–11.
32. Lin L, Xu C. Arcsine-based transformations for meta-analysis of proportions: pros, cons, and alternatives. Health Sci Rep 2020; 3:e178.
33. Barendregt JJ, Doi SA, Lee YY, Norman RE, Vos T. Meta-analysis of prevalence. J Epidemiol Community Health 2013; 67:974–8.
34. Cliff A, Ord J. Spatial autocorrelation. Vol. 19. Methuen, New York: SAGE Publications Ltd, 1973.
35. Goodchild MF. Spatial autocorrelation. Norwich: Geo Books, 1986:56.
36. Anselin L, Sridharan S, Gholston S. Using exploratory spatial data analysis to leverage social indicator databases: the discovery of interesting patterns. Soc Indic Res 2007; 82:287–309.
37. Griffith D. Gaining understanding through theory and scientific visualization. In: Spatial autocorrelation and spatial filtering. Berlin: Springer, 2003. https://www.springer.com/gp/book/9783540009320. Accessed 19 January 2021.
38. Wubuli A, Xue F, Jiang D, Yao X, Upur H, Wushouer Q. Socio-demographic predictors and distribution of...
pulmonary tuberculosis (TB) in Xinjiang, China: a spatial analysis. PLoS One 2015; 10:e0144010.

39. XLSTAT. Ordinary least squares regression (OLS). https://www.xlstat.com/en/solutions/features/ordinary-least-squares-regression-ols. Accessed 4 January 2021.

40. ArcGIS. Ordinary least squares (OLS). 2021. https://desktop.arcgis.com/en/arcmap/10.3/tools/spatial-statistics-toolbox/ordinary-least-squares.htm. Accessed 9 January 2021.

41. Fotheringham AS, Brunsdon C. Local forms of spatial analysis. Geogr Anal 1999; 31:340–58.

42. Duarte-Cunha M, Almeida AS, Cunha GM, Souza-Santos R. Geographic weighted regression: applicability to epidemiological studies of leprosy. Rev Soc Bras Med Trop 2016; 49:74–82.

43. ScienceDirect. Geographically weighted regression—an overview. 2021. https://www.sciencedirect.com/topics/earth-and-planetary-sciences/geographically-weighted-regression. Accessed 9 January 2021.

44. Ge Y, Song Y, Wang J, et al. Geographically weighted regression-based determinants of malaria incidences in northern China. Trans GIS 2017; 21: 934–53.

45. Haque U, Scott LM, Hashizume M, et al. Modelling malaria treatment practices in Bangladesh using spatial statistics. Malar J 2012; 11:63.

46. Esri. ArcGIS Pro—how spatial autocorrelation (global Moran's I) works. https://pro.arcgis.com/en/pro-app/2.7/tool-reference/spatial-statistics/h-how-spatial-autocorrelation-moran-s-i-spatial-st.htm. Accessed 4 July 2021.

47. Alam M. Spatial autocorrelation: neighbors affecting neighbors. 2020. https://towardsdatascience.com/spatial-autocorrelation-neighbors-affecting-neighbors-ed4fab8a4aac. Accessed 4 July 2021.

48. Gasem MH, Dolmans WM, Keuter MM, Djokomoejanto RR. Poor food hygiene and housing as risk factors for typhoid fever in Semarang, Indonesia. Trop Med Int Health 2001; 6:484–90.

49. Lee JS, Mogasale VV, Mogasale V, Lee K. Geographical distribution of typhoid risk factors in low and middle income countries. BMC Infect Dis 2016; 16:732.

50. Osei FB, Stein A, Nyadanu SD. Spatial and temporal heterogeneities of district-level typhoid morbidities in Ghana: a requisite insight for informed public health response. PLoS One 2018; 13:e0208006.