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GEOGRAPHICAL DISTRIBUTION AND RISK FACTORS ASSOCIATED WITH ENTERIC DISEASES IN VIETNAM

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Abstract. In Vietnam, shigellosis, typhoid fever, and cholera are important enteric diseases. To determine their magnitude and geographical distribution, and explore associated risk factors, we examined national surveillance data from 1991 to 2001 and potential ecological determinants. Average annual incidence rates were calculated and mapped for each province. Bivariate and multiple regression analyses were used to explore associations with selected environmental and human risk factors. Overall, shigellosis rates per 100,000 population (median, 41; mean, 70) were higher and more widespread than rates for typhoid fever (median, 7; mean, 23) and cholera (median, 0.3; mean, 2.7). Shigellosis was highest in the Central Highlands and was significantly associated with rainfall and urban poverty; typhoid fever prevailed in the Mekong River Delta and was most associated with vapor pressure and river/stream drinking water; and cholera predominated along the Central Coastal regions and correlated positively with rainfall and public well drinking water. The distinct geographical patterns of each disease appear to be driven by a combination of different ecological factors.

INTRODUCTION

Enteric diseases cause considerable morbidity and mortality worldwide, especially among children in developing countries.[1–5] Shigellosis (bacillary dysentery), typhoid fever, and cholera are severe diseases caused by the pathogens *Shigella* spp., *Salmonella typhi*, and *Vibrio cholerae,* respectively. The causative microbes are environmentally determined, with transmission occurring through fecal contamination of food or water or by person-to-person contact. Infection rates are highest where general standards of living, water supply, and sanitary conditions are low or inadequate.

Shigella spp. are the most common cause of dysentery, and shigellosis is a debilitating, potentially fatal disease characterized by a rapid onset of diarrhea (often bloody), fever, and abdominal cramps.[1] Four species can cause this disease: *S. dysenteriae, S. flexneri, S. boydii,* and *S. sonnei.* In developing countries, *S. flexneri* is the most common, while *S. dysenteriae* is the most severe and main cause of epidemics. Typhoid fever is an infectious bacterial disease characterized by prolonged high fever, headache, abdominal pain, rash, and either diarrhea or constipation.[2,5] Severely ill individuals may experience delirium, shock, and intestinal hemorrhage. Cholera is an epidemic diarrheal disease caused by two serogroups of bacterium (01 and 0139 'Bengal').[3] Symptoms appear abruptly and include nausea, vomiting, intestinal cramping with little or no fever, followed by profuse, painless, watery diarrhea that may exceed 5–10 L per day. Individuals can die rapidly from severe dehydration, hypovolemia, and shock.

The precise burden of these enteric diseases is difficult to establish as they occur in resource-poor countries where substantial under-reporting takes place.[4] Recent studies estimate that 164 million episodes of shigellosis[1] and 22 million each of typhoid fever[2] and cholera[4] occur globally each year, with Africa and Asia being the most affected regions.[6] Antimicrobial treatment can reduce morbidity, mortality, and transmission, but in recent decades these diseases have become increasingly resistant to the most widely used and inexpensive antimicrobials.[7,8] Vaccines are available for typhoid fever and cholera; however, their distribution and long-term efficacy are often limited.[5,9–13] Currently, no vaccine is licensed for *Shigella* spp. outside of China.

In Vietnam, all three diseases raise significant public health concerns.[10] A high incidence of shigellosis, especially *S. flexneri,* has been found to have increasing resistance to antibiotics in all species.[14–21] Typhoid fever has frequently been reported in the Mekong River Delta[14,22–24] and more recently in the northwest region.[25] Contact with typhoid patients, contaminated food, and water have been identified as important risk factors,[24–26] and drug resistance has become a serious problem[27–34] with multidrug-resistant *S. typhi* a major cause of community-acquired septicemia.[32] In Vietnam, outbreaks of cholera have occurred for over a century.[35] In this century's seventh pandemic, *V. cholerae* 01 (El Tor) appeared in 1964, causing an epidemic affecting over 20,000 people with subsequent widespread and long-lasting activity.[25] Strains of *V. cholerae* 01 remain the only biotype in Vietnam,[36] and although selected antibiotics remain effective,[37] this pathogen and *V. cholerae* 0139 are being targeted with new vaccines.[38–40]

Currently, there is interest to better define the global burden of diarrheal diseases and implement programs that use specific interventions for specific microbes.[4] Given that disease distributions vary over space and time, epidemiologic patterns can be examined by two main ways: routine surveillance data and detailed prospective population studies. The latter method is time-consuming, costly, and logistically unrealistic if national trends and high-risk regions are to be determined. However, national surveillance data provide a low-cost, practical alternative in which to first explore the epidemiology and can provide the basis for more specific studies to be undertaken in high-risk areas. Although surveillance data are limited because the degrees of reporting bias, misdiagnosis, and misclassification are unknown, assessment of government data is considered worthwhile because policy decisions may be based on them.

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In Vietnam, data on shigellosis/dysentery, typhoid fever, and cholera have been collated for each province from 1991 to 2001. To explore epidemiologic patterns across the country, we use this subnational data to describe the magnitude and geographical distribution of each disease and to examine potential environmental and human risk factors.

METHODS

Study location. The Socialist Republic of Vietnam has approximately 83,535,600 people living an area of 329,560 km^2 with 3,444 km of coastline.[41] It is a narrow, densely-populated, rapidly developing country in Southeastern Asia bordering China, Laos, and Cambodia (Figure 1). The climate is tropical in the south, and in the north are two basic seasons: a warm, wet summer and a cool, humid winter. The terrain is extremely diverse with low-lying deltas in south and north, highlands in the central region, and hilly mountains in far northwest. Most of the labor force is used in agriculture, with paddy rice, coffee, and seafood among the main products.

During the 1990s, the provincial borders were changed, with two larger provinces in 1992 and eight in 1996 each being divided into smaller ones.[42] This resulted in a total of 61 provinces, which were grouped into eight regions (Figure 1)[43] and are the basis of our analyses as corresponding geographical boundaries, national survey, and environmental data were available.

Data sources and analyses. To determine the magnitude and geographical distribution of each disease, average annual incidence rates (IRs) per 100,000 population were calculated for each province and mapped using the geographical information system software ArcGIS 9.1 (ESRI, Redlands, CA). Geographical patterns were assessed for evidence of spatial autocorrelation using the Moran's *I* statistic to determine the extent to which they were clustered, dispersed, or random.[44]

Data on shigellosis/dysentery, typhoid fever, and cholera for each province in Vietnam from 1991 to 2001 were obtained from the Epidemiology Department, National Institute of Hygiene and Epidemiology, Hanoi, and a central database managed by the International Vaccine Institute, Korea. Data were based on treated episodes with data routinely collected by District Health Centers as part of the Vietnam Ministry of Health surveillance system and supplemented with data reported in published scientific literature and unpublished national health reports; thus a combination of clinically diagnosed and serologically and stool culture confirmed cases were studied. To account for provincial changes during the study period, cases reported before the divisions were disaggregated proportionally based on subsequent years' disease data. Population data for the years 1995 to 2001 were obtained from the General Statistics Office of Vietnam,[43] with estimates for 1991 to 1994 extrapolated from the fitted cubic spline of the known years, using MATLAB software (The MathWorks, Inc., Natick, MA).

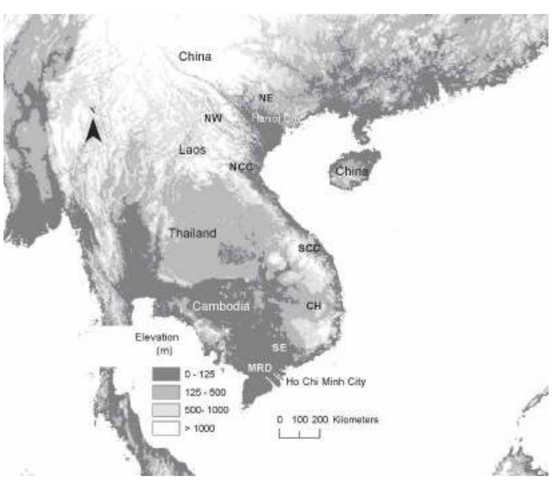

FIGURE 1. Vietnam and its eight regions: RRD, Red River Delta; NE, North East; NW, North West; NCC, North Central Coast; SSC, South Central Coast; CH, Central Highlands; SE, South East; MRD, Mekong River Delta. (Image source: ESRI, Redlands, CA.)

To explore possible risk factors of each disease, we selected environmental and human factors potentially important in transmission that could readily be examined at the provincial level. Variables included latitude, altitude, rainfall, temperature, vapor pressure, land use, population density, poverty, water sources, and toilet facilities and were obtained from the best-available sources. In ArcGIS 9.1, latitude was determined from the midpoint of each province, and the average altitude of main populations from the U.S. Geological Survey's digital elevation data. Climate data were obtained from worldwide maps generated by the interpolation of information from ground-based meteorological stations with a monthly temporal resolution and 0.5° (latitude) by 0.5° (longitude) spatial resolution.[45] Rainfall, temperature, and vapor pressure values were extracted from the pixels containing the centroid of each province, using Matlab software.

Population estimates, land use, poverty, water, and sanitation information were based on national statistics and survey data. Population density and the percent of agricultural and forested land in each province were obtained from the General Statistics Office of Vietnam.[43] A recent comprehensive report on poverty and inequity, which combined data from the 1997–1998 Vietnam Living Standards Survey, and the 1999 Population and Housing Census provided estimates of overall, rural, and urban poverty.[46] Information on drinking water sources and toilet facilities were extracted from the Vietnam Living Standard Survey 1997–1998, obtained from the Demographic and Health Surveys database (http://www.measuredhs.com/). Data were only available for 41 provinces and included the proportion of people whose main drinking water source was piped water in residence, public tap, well in residence, spring, river/stream, pond/lake, and rainwater and whose main toilet facility was own flushed, shared flushed, traditional or ventilated pit latrine, and no facility/bush.

For each disease, the total number of cases, average annual IRs (median and mean per 100,000) and regions and provinces with the highest and lowest rates were identified. The relationship between average shigellosis/dysentery, typhoid fever, and cholera IRs (mean/100,000) and each determinant was examined using bivariate correlation and Pearson's correlation coefficient (2-tailed P value $\leq$ 0.05 significance). Stepwise multiple linear regression analysis was used to identify determinants (independent variables) that would best predict the rate of each disease. To avoid variables that were highly correlated ($r \geq 0.8$) with each other, i.e., eliminate the collinearity risk, Pearson's correlation was conducted between the independent variables, which resulted in latitude, agricultural land, overall poverty, and own flush toilet being excluded from the multivariate analysis. To further account for collinearity, the level of collinearity tolerance in the stepwise regression procedure was set at ≥ 0.8, and only variables above this threshold were accepted in models. All statistical analyses were performed in Microsoft Excel and SPSS 13.0 (SPSS, Inc., Chicago, IL).

RESULTS

Shigellosis/dysentery. Overall, the incidence of shigellosis/dysentery was higher and more widespread than that of typhoid fever and cholera (Figure 2). During the study period, 435,037 total shigellosis/dysentery cases (~39,500 per annum) were reported nationally, with the highest numbers recorded in the Mekong River Delta (28.2%), South Central Coast (15.9%), and Central Highlands (14.7%). The national average annual IR was between 40.8 (median) and 70.0 (mean)/100,000. The highest annual rates occurred in the Central Highlands (median, 156.0; mean, 241.7; per 100,000) and on the South Central Coast (median, 116.4; mean, 100.2), with the provinces Kon Tum (median, 576.5; mean, 613.8) and Khanh Hoa (median, 220.8; mean, 52.2) recording the highest rates in each region, respectively. Overall, the lowest rates occurred in the Red River Delta (median, 15.4; mean, 20.9; per 100,000) region, with Ha Noi recording the lowest rates (0–0.68) of shigellosis/dysentery for the country. The Moran's $I = 0.14$ ($P < 0.01$) statistic indicates significant levels of positive spatial autocorrelation or clustering, as shown in Figure 2.

Bivariate correlations shown in Table 1 indicate that shigellosis/dysentery incidence was most significantly associated with altitude, rainfall, vapor pressure, and no toilet/bush facilities. Urban poverty and public well drinking water were also positively associated with disease; however, latitude, population density, and traditional and ventilated pit latrines were negatively correlated. Variables with nonsignificant P values were kept in the multivariate analysis because they improved the regression models. Multiple regression analysis indicated that rainfall and urban poverty were important variables, explaining 60% ($R^2 = 0.602$, F = 28.74, $P = 0.000$) of the variance in the model (Table 2).

Typhoid fever. A total of 187,318 typhoid fever cases (~17,000 per annum) were reported nationally between 1991 and 2001. The highest numbers were recorded in the Mekong River Delta (75.8%), and South East (6.9%). The national average annual IR was between 6.7 (median) and 23.3 (mean) per 100,000. The highest annual rates occurred in the Mekong River Delta (median, 77.6; mean, 78.8 mean; per 100,000) and in the North West (median, 38.0; mean, 34.5), with the province Dong Thap (median, 109.9; mean, 199.5) and Lai Chau (median, 20.9; mean, 63.9) recording the highest rates in each region, respectively (Figure 2). Overall, the lowest rates occurred in the North East (median, 0.3; mean, 2.7; per 100,000), with the province Yen Bai recording no cases of typhoid fever during the study period. The Moran's $I = 0.27$ ($P < 0.01$)

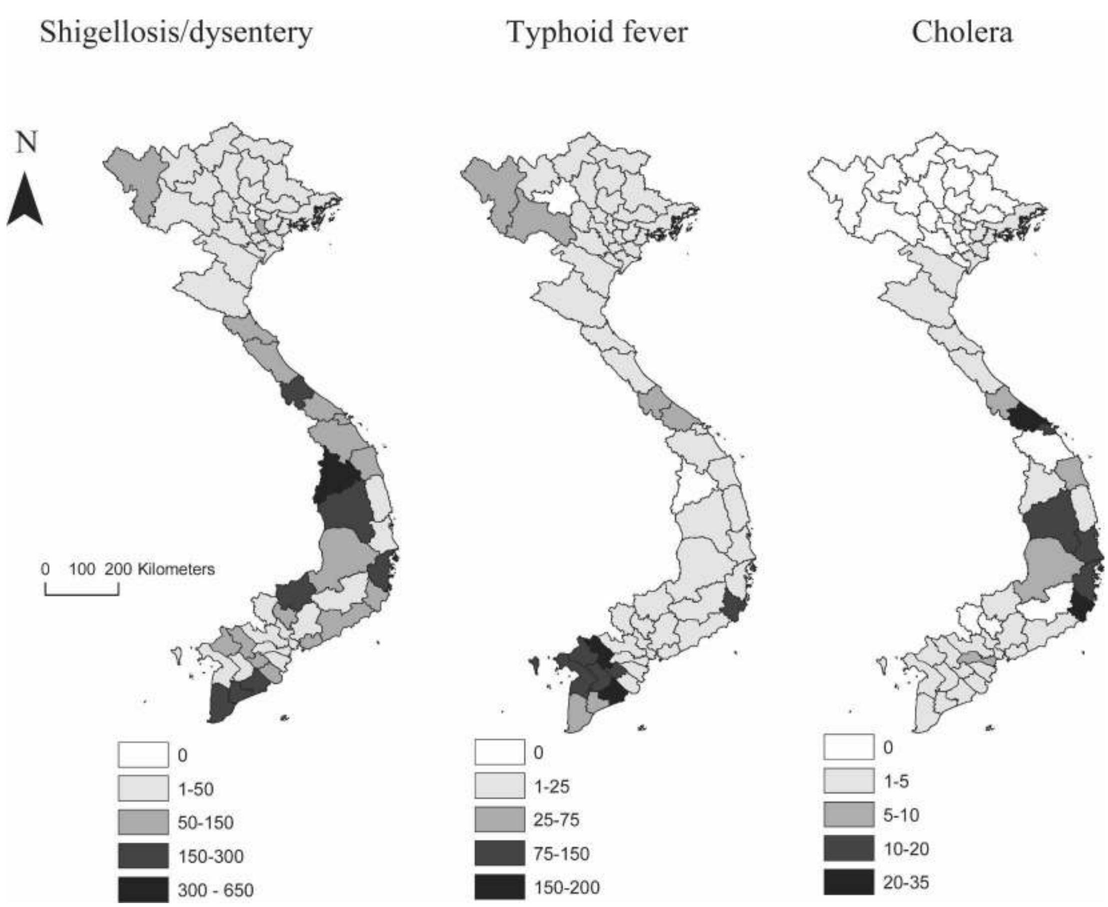

FIGURE 2. Shigellosis/dysentery, typhoid fever, and cholera average annual incidence rates per 100,000 population.

TABLE 1

Bivariate analysis of shigellosis/dysentery, typhoid fever, and cholera average annual incidence rates per 100,000 and selected variables

Variable	Correlation (P value)		
	Shigellosis/dysentery	Typhoid fever	Cholera
Environmental			
Latitude	–0.32 (0.013)*	–0.49 (0.00)**	–0.21 (0.107)
Altitude	0.34 (0.008)**	–0.20 (0.117)	–0.09 (0.502)
Rainfall	0.40 (0.001)**	0.35 (0.006)**	0.37 (0.003)**
Temperature	0.10 (0.434)	0.49 (0.000)**	0.03 (0.820)
Vapor pressure	0.40 (0.002)**	0.49 (0.000)**	0.29 (0.025)*
Forested land	0.23 (0.074)	–0.34 (0.007)**	0.23 (0.076)
Agricultural land	–0.10 (0.438)	0.41 (0.001)**	–0.26 (0.043)*
Population and poverty			
Population density	–0.28 (0.027)*	–0.08 (0.546)	–0.14 (0.272)
Overall poverty	0.03 (0.800)	0.06 (0.664)	0.02 (0.916)
Urban poverty	0.27 (0.039)*	0.36 (0.004)**	0.20 (0.132)
Rural poverty	0.10 (0.461)	0.04 (0.769)	0.10 (0.460)
Source of drinking water			
Piped into residence	–0.09 (0.598)	–0.09 (0.587)	0.19 (0.246)
Public tap	–0.14 (0.381)	–0.21 (0.198)	0.20 (0.211)
Well in residence	0.02 (0.920)	–0.35 (0.025)*	–0.21 (0.180)
Public well	0.35 (0.025)*	0.00 (0.986)	0.42 (0.006)**
Spring	–0.08 (0.629)	–0.04 (0.821)	–0.09 (0.571)
River/stream	0.09 (0.594)	0.55 (0.000)**	0.23 (0.162)
Pond/lake	0.30 (0.057)	0.29 (0.063)	0.18 (0.263)
Rain water	–0.09 (0.580)	0.06 (0.728)	–0.19 (0.244)
Type of toilet facility			
Own flush toilet	0.08 (0.617)	–0.08 (0.642)	0.28 (0.075)
Shared flush toilet	–0.30 (0.053)	–0.05 (0.751)	–0.16 (0.314)
Traditional pit latrine	–0.31 (0.047)*	–0.09 (0.578)	–0.37 (0.018)*
Ventilated pit latrine	–0.33 (0.036)*	–0.36 (0.021)*	–0.14 (0.398)
No facility/bush	0.41 (0.007)**	0.32 (0.044)*	0.21 (0.186)
Other diseases			
Cholera	0.23 (0.076)	0.12 (0.335)	
Typhoid	0.15 (0.240)		

* Correlation significant at $P < 0.05$.
** Correlation significant at $P < 0.01$.

statistic indicates significant levels of geographical variation and clustering, as shown in Figure 2.

Bivariate correlations shown in Table 1 indicate that typhoid fever incidence was positively associated with rainfall, temperature, vapor pressure, agricultural land, urban poverty, river/stream drinking water, and no toilet/bush facilities but was significantly negatively correlated with latitude, forested land, well in residence drinking water, and ventilated pit latrines. Multiple regression analysis indicated that vapor pressure and river/stream drinking water and the lack of forested land and public tap drinking water were important predictors, explaining 64.2% ($R^2 = 0.642$, F = 16.12, $P = 0.000$) of the variance in the model (Table 2).

TABLE 2

Stepwise multiple linear regression models predicting average annual incidence rates of shigellosis/dysentery, typhoid fever, and cholera (across 61 provinces)

Disease/predictor variables	Standardized coefficient beta	t statistic	p value	Collinearity tolerance
Shigellosis				
(Constant)		–5.754	0.000	
Rainfall	0.589	5.532	0.000	0.923
Urban poverty	0.368	3.451	0.001	0.923
Typhoid fever				
(Constant)		–4.397	0.000	
Vapor pressure	0.535	5.135	0.000	0.915
River/stream drinking water	0.374	3.541	0.001	0.893
Forested land	–0.312	–2.958	0.005	0.896
Public tap drinking water	–0.210	–2.094	0.043	0.989
Cholera				
(Constant)		–3.042	0.004	
Rainfall	0.417	3.117	0.003	0.963
Public well drinking water	0.340	2.544	0.015	0.963

Note. Shigellosis $R^2 = 0.602$ (adjusted $R^2 = 0.581$), F = 28.74 $P = 0.000$; Typhoid fever $R^2 = 0.642$ (adjusted $R^2 = 0.602$), F = 16.12 $P = 0.000$; Cholera $R^2 = 0.345$ (adjusted $R^2 = 0.310$), F = 9.99 $P = 0.000$.

Cholera. Cholera was the least-prevalent disease, with a total of 17,385 cases (~1,580 per annum) reported nationally between 1991 and 2001. Cases were episodic and most were reported before 1997. The highest numbers were recorded on the South Central (28.4%) and North Central (27.1%) coasts. The national average annual IR was between 0.3 (median) and 2.7 (mean) per 100,000. The highest annual rates occurred in the South Central (median, 8.5; mean, 8.6; per 100,000) and North Central (median, 2.7; mean, 7.6) coasts, with the province Khanh Hoa (0–17.7) and Thua Thien-Hue (0–33.5) recording the highest rates in each region, respectively (Figure 2). No cases of cholera were recorded in the North East or North West during the study period, except for the province Quang Ninh (0.0–0.9), where 96 cases occurred in 1995–1996. The Moran's $I = 0.12$ ($P < 0.01$) statistic indicates significant levels of positive spatial autocorrelation or clustering, as shown in Figure 2.

Bivariate correlations shown in Table 1 indicate that cholera incidence was positively associated with rainfall, vapor pressure, and public well drinking water and significantly negatively correlated with agricultural land and traditional pit latrine. Multiple regression analysis indicated that high rainfall and public well drinking water were the most important variables, explaining 34.5% (R^2 = 0.345, F = 10.0, P = 0.000) of the variance in the model (Table 2).

DISCUSSION

This study shows that reported shigellosis/dysentery, typhoid fever, and cholera have different geographical patterns in Vietnam, and their prevalence and distribution may be associated with a combination of different ecological factors. Overall, shigellosis/dysentery was the most reported disease with ~435,000 cases from 1991 to 2001, compared with 187,000 typhoid fever and 17,000 cholera cases. Nearly half (45%) of the shigellosis/dysentery cases occurred in the southern Mekong River Delta and South Central Coast regions; however, the highest rates occurred in the Central Highlands, close to the Laos and Cambodia border where rainfall and poverty are among the highest in the country.[43,46] Statistical analyses suggest that high rainfall and urban poverty are the most significant risk factors of shigellosis/dysentery; however, vapor pressure, public well drinking water, and no toilet/bush facilities also appear to be important. *Shigella* spp. can seep into groundwater and drinking wells through discharges from faulty septic or sewage systems. Wells can also become contaminated after flooding, particularly if they are shallow or hand dug, as they are in Vietnam.[43] In the highland province of Dak Lak, water from dug wells has shown a higher risk of fecal contamination than water from mixed wells or boreholes.[47]

The wide distribution of shigellosis/dysentery may also be attributed to the different *Shigella* spp. and their ability to thrive in a range of ecological niches. Overall, *S. flexneri* and *S. sonnei* are the most frequently isolated species in Vietnam[15,17,18]; however, a significantly higher prevalence of *S. boydii* (17%) was recently found along the Red River than in previous decades (3%).[19] In addition, *S. flexneri* serotypes may have changed since the 1960s when types 2, 3, 1, and 4 (66%, 16%, 10%, and 5%, respectively) were identified, compared with recent years when types 6, 1, and 4, and variant Y (17%, 13%, 10%, and 9%, respectively) predominated and 40% of *S. flexneri* isolates could not be serotyped using commercial kits. This suggests that there may be new variants and that *Shigella* spp. are dynamic and able to survive in diverse environmental conditions at different times. This, coupled with widespread antibiotic resistance,[17–21] may account for the ubiquitous nature of shigellosis/dysentery in Vietnam and highlights the potential difficulty in targeting individual *Shigella* species and serotypes with type-specific vaccines. It is also possible that the reported dysentery is caused by other pathogens, such as *Campylobacter* and *Escherichia coli,* which are prevalent in Vietnam[19,21,48] and suggests that better case definition and diagnostic tools may be required for this particular enteric syndrome.

The distribution of typhoid fever is distinct to that of shigellosis/dysentery and cholera, with the majority of cases (75%) and highest rates found in the southern Mekong River Delta. Although high numbers of typhoid fever and shigellosis/dysentery coincide in this tropical delta region, we found typhoid fever to be relatively absent from central Vietnam, especially in the highlands where shigellosis/dysentery also prevailed. This is consistent with previous findings where typhoid fever was more prevalent in densely populated agricultural lowlands than in sparsely populated mountainous forest regions.[22] Our multivariate analysis identified high vapor pressure and river/stream drinking water to be positively related but forested regions and public tap drinking water to be negatively associated with typhoid fever, which may explain the lack of disease in the Central Highlands where over 50% of the land is forested and the climate is cooler and less humid than the tropical Mekong River Delta.

Other factors pertaining to the Mekong River Delta may also influence typhoid fever transmission. Typhoid fever is endemic in this agricultural region, and peak periods have occurred prior to the rainy season, when river levels are low,[24,26] which may be related to scarcity of water and compromised hygiene practices, especially as most people live and work by paddy fields and river tributaries, using them for both drinking water and sanitation.[23,26] Recent national survey data indicate that ~42% of people in the Mekong River Delta use rivers, lakes, springs, or ponds as their main water sources compared with < 4% in other regions.[43] In addition, 68% of people have their toilet facilities directly over water compared with < 4% in other regions where pit latrines, flush toilets, and other facilities are more frequently used. This link between open, untreated water sources and human excrement may explain why typhoid fever is highest in this region.

A similar finding was noted in a typhoid fever case-control study in the northern province of Son La, where cases were four times more likely to drink untreated water from wells or streams and dispose sewage directly into the environment than were controls.[25] This study also identified close contact with a typhoid case and no schooling as key determinants. Typhoid fever is endemic in the south and has only recently become a public health concern in the North West.[25] Epidemics have been reported in Son La since 1998, and we found high rates of disease in the far northwest provinces. The reasons for the increase in this remote rural region is unclear but may be related to the opening of the border and freer trade with China, which occurred in the late 1990s.

Interestingly, cholera was not reported in the far northwest mountainous region during the study period. We found cholera distribution to be more confined to the central region of Vietnam and overlapped with shigellosis/dysentery rather than with typhoid fever. The highest numbers (55.5%) and rates of cholera were found in the North Central and South Central coasts, and our statistical analyses suggest that rainfall and public well drinking water may be important risk factors. As shown elsewhere, it is also possible that such factors as sea surface temperature and height[49] may impact cholera patterns in coastal regions. Further, we found that high rates of cholera in Vietnam were not associated with agricultural land, a trend also evident with shigellosis/dysentery, which may explain why their distributions coincide. Recent outbreaks of cholera have been reported from urban areas,[35,36] and in 1997 a new locally produced vaccine targeting both *V. cholerae* 01 and 0139 pathogens, was introduced into high-risk populations.[38,50] Since then, this vaccine has been integrated into the national immunization program; although the overall epidemiologic impact is yet to be determined, this intervention may change future distributions of cholera in Vietnam.[40]

Our analyses also indicate that provision of basic sanitation facilities may be protective against shigellosis/dysentery, typhoid fever, and cholera, which supports existing literature.[51] Although we found certain water sources and the lack of toilet facilities associated with each disease, the significant negative associations with pit latrines and flush toilets suggest that they help to reduce transmission. Water, hygiene, and sanitation interventions are important factors in reducing the incidence of diarrhea, and these have been shown to be cost-effective.[51] Although there is interest to target these diseases with vaccines, efforts to control the diseases should also focus on improvement of water supply, personal hygiene, and sanitation facilities.

We acknowledge that the main limitations of this study are related to the quality of the surveillance data and analysis of risk factors at provincial level. Surveillance data worldwide rely on the quality of reporting, and the degree of reporting bias, misdiagnosis, and misclassification are often unknown. The diseases in this study are reportable and therefore should be complete; however, detection is not simple, and adequate diagnostic facilities are not universally available throughout Vietnam. Detection may be biased toward centers with diagnostic facilities or to those individuals with severe symptoms or better access to health centers. Although these diseases differ symptomatically from each other, and therefore are clinically distinguishable, shigellosis and dysentery are used synonymously, and typhoid fever has a similar presentation to paratyphoid fever (representing ~10–25% of enteric fevers),[52] and serological tests are nonspecific.[5] Cholera is often associated with outbreaks and is more readily detected than endemic cholera, so the true extent of this disease may be underestimated; provincial centers, however, have the capacity to analyze stool samples for *V. cholerae*.[35]

We also recognize that there are problems with making several statistical tests simultaneously, and our risk-factor analyses at the provincial level may lead to spurious associations.[53] Therefore, results can only provide preliminary insights into the ecology of these diseases and must be interpreted with caution. Finally, we acknowledge that spatial regression models could have been used to further increase the R^2 values. However, the resolution of the data in this exploratory study is probably not appropriate for such complicated statistical models and therefore was considered to be beyond the scope of this paper. Future work using more accurate data collection on a finer scale (district level) would be better for investigating the spatial correlation and spatial variability among the measured associations.

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