1. Introduction

Cholera is an acute intestinal infection caused by the water borne bacteria *Vibrio cholerae* O1 or O139 (*V. cholerae*). Infection is mainly through ingestion of contaminated water or food (Kelly, 2001). Approximately $10^2$-$10^3$ cells are required to cause severe diarrhea and dehydration (Sack et al., 1998; Hornich et al., 1971). Ingested cholera vibrios from contaminated water or food must pass through the acid stomach before they are able to colonize the upper part of the small intestine. After penetrating the mucus layer, *V. cholerae* colonizes the epithelial lining of the gut, secreting cholera toxin which affects the small intestine.

Clinically, the majority of cholera episodes are characterized by a sudden onset of massive diarrhea and vomiting. This is accompanied by the loss of profuse amounts of protein-free fluid along with electrolytes, bicarbonates and ions. The resulting dehydration produces tachycardia, hypotension, and vascular collapse, which can lead to sudden death. The diagnosis of cholera is commonly established by isolating the causative organism from the stools of infected individuals. The main mode of treatment is the replacement of electrolyte loss through the intake of a rehydration fluid, i.e. Oral Rehydration Salts (ORS) (Sack et al., 2004). Without prompt treatment, fatality rate can be as high as 50% (WHO, 1993; Sack et al., 2004). With adequate treatment, i.e. intravenous and oral rehydration therapy, supplemented with appropriate antibiotics, the fatality rate can drop to approximately 1.0% (Carpenter et al., 1966; Mahalanabis et al., 1992).

In its extreme manifestation, cholera is one of the most rapidly fatal infectious illnesses known. Within 3–4 hours of onset of symptoms, a previously healthy person may become severely dehydrated and if not treated may die within 24 hours (WHO, 2010). The disease is one of the most researched in the world today; nevertheless, it is still an important public health problem despite more than a century of study, especially in developing tropical countries. Cholera is currently listed as one of three internationally quarantinable diseases by the World Health Organization (WHO), along with plague and yellow fever (WHO, 2000a). The growing number and frequency of major cholera outbreaks, especially in
countries on the African continent, have heightened concerns of focusing epidemiological research on the underlying risk factors and the identification of high risk areas.

Using simple geographical mapping, John Snow (1855) first associated cholera with contaminated drinking water in the 1850s even before any bacterium was known to exist. After Snow’s seminal work, most epidemiological studies of cholera have focused on the pathogenesis and biological characteristics of *V. cholerae* (Yamai et al., 1977; Faruque et al., 1998; Ramamurthy et al., 1993; Felsenfeld, 1966; Singleton et al., 1982a, 1982b; Colwell et al., 1977; Barua and Paguio, 1977; Glass et al., 1985). However useful these studies are, they usually cannot establish accurate individual exposure levels for the critical risk factors of the disease (Haining, 1998). Spatial epidemiological tools applied in cholera studies can facilitate the identification of high risk areas and the formulation of hypotheses about the causal factors responsible for such variations, as well as the optimal allocation of health facilities to improve health care provision. The objective of this study is to present from published literature the general epidemiology of cholera, its spatial epidemiology as well as important spatial epidemiologic tools utilized in cholera studies.

### 2. Biology and ecology of *V. cholerae*

The biology and ecology of *V. cholerae* has been described by many authors (Yamai et al., 1977; Faruque et al., 1998; Ramamurthy et al., 1993; Felsenfeld, 1966; Singleton et al., 1982a, 1982b; Colwell et al., 1977; Barua and Paguio, 1977; Glass et al., 1985). *V. cholerae* is an aerobic, motile, Gram-negative rod that is shaped like a comma (Hamer and Cash, 1999). When ingested in the body, *V. cholerae* produces an exotoxin that either stimulates the mucosal cells to secrete large quantities of isotonic fluid, or increases the permeability of the vascular endothelium, thus allowing isotonic fluid to pass through in abnormal amount, resulting in watery diarrhea.

*V. cholerae* is differentiated serologically by the O antigen of its lipopolysaccharide. Over 200 serogroups of *V. cholerae* have been documented (Yamai et al., 1997). The toxigenic *V. cholerae* serogroups, which cause epidemic cholera, are the O1 and O139 (Faruque et al., 1998). Until 1992 when a newly serogroup designated O139 was identified after unusual outbreaks in India and Bangladesh (Ramamurthy et al., 1993), only the O1 serogroup was known to cause epidemic. The two major biotypes of the *V. cholerae* O1 serogroup are the classical and the El Tor (named after the El Tor quarantine camp on the Sinai peninsula where it was first isolated in 1905 from the intestines of pilgrims returning from Mecca) (Hamer and Cash, 1999). Admirably, *V. cholerae* O1 infection induces adaptive immune responses that are protective against subsequent infection. Volunteer studies in non-endemic regions have demonstrated that infection with classical biotype of *V. cholerae* O1 provides 100% protection for 3 years from subsequent challenge with a classical biotype strain, while infection with the El Tor biotype of *V. cholerae* O1 provides 90% protection for 3 years from subsequent challenge with an El Tor strain (Levine et al., 1981). In an endemic region, an initial episode of El Tor cholera reduces the risk of a second clinically apparent infection by 90% over the next several years (Glass et al., 1982).

The general assumption by most workers, until the mid 1960’s, was that *V. cholerae* was an organism whose normal habitat was the human gut and/or intestine, and incapable of surviving for more than a few days outside the gut (Falsenfeld, 1966). *V. cholerae* is now
known to be a water-borne bacterium that is natural inhabitant of brackish aquatic environments, which survives and multiplies in association with zooplankton and phytoplankton, quite independently of infected human beings (Colwell and Spira, 1993; Colwell and Huq, 1994; Islam et al; 1994; Nair et al., 1988; Huq et al., 1983; Islam et al., 1990). Colwell et al. (1977) first proposed that \textit{V. cholerae} is ecologically autochthonous in estuarine and coastal waters. Colwell et al. (1977, 1980) isolated \textit{V. cholerae} from plankton samples from Bangladesh waters and Chesapeake Bay (United States) and suggested that an association between \textit{V. cholerae} and chitinous plankton may exist. Survival of \textit{V. cholerae} in the aquatic environment, abundance and expression of virulence factors including cholera toxin (CT), and colonization factors such as the toxin-coregulated pilus (TCP), are strongly influenced by both biotic and abiotic factors. Abiotic factors such as sunlight, pH, temperature, salinity and nutrients enhance the growth and multiplication of aquatic lives such as phytoplankton and zooplanktons. Sequestration of CO$_2$ during photosynthesis of phytoplankton alter the dissolved O$_2$ and CO$_2$ contents of the surrounding which in turn leads to elevated pH in the estuarine.

3. Epidemiology

3.1 Global distribution

The Ganges Delta region (India) is believed to be the traditional home of cholera from the time of recorded history (Harmer and Cash, 1999). From this region, cholera has spread throughout the world, causing six major pandemics between 1817 and 1961 (Faruque et al., 1998). It is believed that the European invasions of India and India’s fostering of trade with the Dutch Indies spread the disease to other parts of the world. The seventh pandemic, which began in 1961 in Sulawesi, Indonesia, has now involved almost the whole world and is still continuing. The pandemic (i.e. the seventh) reached India in 1964, Africa in 1970 (Barua, 1972; Cvjetanovic and Barua, 1972; Goodgame and Greenough, 1975; Küstner et al., 1981, Glass et al., 1991), southern Europe in 1970 (Editorial, 1971), and South America in 1991 (Swerdlow et al., 1992; Weil and Berche, 1992). The seventh pandemic was confined in Asia for nearly 10 years which later reached the west coast of Africa, the south coast of Europe, and the western Pacific islands in 1970. The seventh pandemic reached the Americas in 1991, starting from the Peruvian coast (Blake, 1994). The fifth and the sixth pandemics epidemiologically incriminated the classical biotype as the causative agent. The earlier pandemics are also believed to have been caused by the classical biotype as well, although there is no hard evidence. The seventh pandemic this time caused by the El Tor biotype has subsequently spread worldwide and largely replaced the classical biotype.

The burden of cholera is characterized by both endemic disease and epidemics. Globally, cholera cases and deaths have increased steadily since the beginning of the 21st century. From 2004 to 2008, a total of 838,315 cases were notified to WHO, compared with 676,651 cases between 2000 and 2004, representing a 24% increase in the number of cases (WHO, 2009). The burden of the disease is currently enormous on developing countries and catastrophically on the African continent. The seventh pandemic is the first to have established persistent residence on the African continent. Africa alone has recorded over 2.4 million cases and 120,000 deaths from 1970 to 2005. This accounts for over 90% of both worldwide cases and deaths (WHO, 2000b, 2001, 2002, 20003, 2004, 2005, 2006). The burden
of the disease on the African continent, however, is possibly worse than officially reported owing to underreporting, limitations in the surveillance and reporting system, as well as fear of unjustified restrictions on travel and trade (WHO, 2000a).

3.2 Transmission hypothesis

Two routes of cholera transmission have been described, primary and secondary transmission. Primary transmission occurs through exposure to an environmental reservoir of *V. cholerae* (Hartley et al., 2006) or contaminated water sources regardless of previously infected persons, and thus responsible for the beginning of initial outbreaks. Primary transmission is enabled by both micro-and macro-level environmental and climatic factors that affect the seasonal patterns of infection (Islam et al., 1994; Alam et al., 2006; Lipp et al., 2002; Sack et al., 2003; Colwell, 1996; Huq and Colwell, 1996; Islam et al, 1989, 1990a, 1990b, 1999). In locations like Africa and South America where one yearly peak of cholera is often observed, the beginning of the epidemics has been associated with environmental conditions that favor the growth and survival of the bacterium (Codeço, 2001; Glass et al., 1991; Swerdlow et al., 1992). Primary transmission appears to play a limited role in the epidemiological process since it does not fully explain the exponential growth of incidences during epidemics.

Secondary transmission or fecal-oral transmission occurs via the fecal-oral route through exposure to contaminated water sources. Fecal-oral transmission provides a mechanism for exhibiting a strong feedback between present and past levels of infection. The importance of fecal-oral transmission in cholera epidemics is also supported by recent time series models fitted to the endemic dynamics of cholera in Bangladesh (Koelle and Pascual, 2004; Koelle et al., 2005). In an epidemic situation, the initial reproduction rate of fecal-oral transmissions is positively affected by the degree of contamination of water supply as well as the frequency of contacts with such contaminated water supply (Codeço, 2001), which in turn is influenced by human dimensions such as local environmental factors, socioeconomic, demographic as well as sanitation conditions. Fecal-oral transmissions reflect a complicated transmission pattern since multiple factors may play a role in the spread of the disease. Although cholera control measures that target primary transmission is clearly important (from the perspective of disease persistence (Colwell et al, 2003)), the dominant role of fecal-oral transmission as observed in several studies (Ali et al., 2002a, 2002b; Mugoya et al., 2008; Borroto and Martinez-Piedra, 2000; Ackers et al., 1998; Sasaki et al., 2008; Sur et al., 2005), suggest that the containment of fecal-oral infections may be a viable and useful strategy to control epidemics.

3.3 Socioeconomic and demographic variations

Socioeconomic and demographic factors have been reported to significantly enhance the vulnerability of a population to infection and contribute to epidemic spread (Ali et al., 2002a, 2002b; Borroto and Martinez-Piedra, 2000; Ackers et al., 1998; Sasaki et al., 2008; Sur et al., 2005). Such factors also mandate the extent to which the disease will reach epidemic proportions (Miller, 1985; Emch et al., 2008) and also modulate the size of the epidemic (Pascual et al., 2002, 2006; Koelle and Pascual, 2004; Hartley et al., 2005). Known population-level (local-level) risk factors of cholera include poverty, lack of development, high population density, low education, and lack of previous exposure (Ackers et al., 1998; Ali et
al., 2002). The synergy of poverty, high population density, poor sanitation, poor housing, and lack of good water supplies enhance exposure to pathogenic cholera vibrios. In epidemic prone regions like Africa, cholera outbreaks have been linked to multiple environmental and socio-economic sources (Acosta et al., 2001; Shapiro et al., 1999). Cholera diffuses rapidly in environments that lack basic infrastructure with regard to access to safe water and proper sanitation. The cholera vibrios can survive and multiply outside the human body and can spread rapidly in environments where living conditions are overcrowded and where there is no safe disposal of solid waste, liquid waste, and human feces (Ali et al., 2002a, 2002b). Root (1997) and Siddique et al (1992) have reported that increase in population density can strain sanitation systems, thus putting people at increased risk of contracting cholera. Ali et al (2002a, 2002b) have identified high population density and low educational status as important risk factors of cholera in an endemic area of Bangladesh.

3.4 Temporal variations

Many researchers have hypothesized the temporal variation of cholera as due to environmental and climatic factors that affect the seasonal patterns of infection (Alam et al., 2006; Lipp et al., 2002; Sack et al., 2003; Colwell and Huq, 2001; Pascual and Dobson, 2005; Huq and Colwell, 1996; Huq et al., 2005; Islam, 1990; Islam et al., 1990, 1993, 1999, 2004). The temporal variation of endemic and epidemic cholera has been associated with both regional and local environmental forces such as rainfall patterns, sea surface temperature and the El Nino Southern Oscillation (Epstein, 1993; Patz et al., 1996; Colwell, 1996; Bouma and Pascual, 2001; Colwell and Huq, 2001; Pascual et al., 2002; Koelle et al., 2005, Huq et al., 2001). Outbreaks in Peru and Bangladesh have been linked to periodic climatic cycles of the El Nino Southern Oscillation (Salazar-Lindo et al., 1997; Pascual et al., 2002; Rodo et al., 2002). In Bangladesh cholera epidemics occur twice a year in the spring and fall, before and after the monsoons (Merson et al., 1980; Islam et al., 1993; Emch and Ali, 2001; Longini et al., 2002). Several studies have also described a regular seasonal cycle of outbreaks in Bangladesh, including specific studies on the different strains: classical (Samadi et al., 1984), El Tor (Khan et al., 1984) and O139 (Alam et al., 2006). Temporal variation of cholera has also been related to variations in physical and nutritional aquatic parameters, including conditions in both coastal and estuarine environments (Faruque et al., 2005). Studies in Bangladesh have also shown environmental associations with V. cholerae, including water temperature and depth, rainfall, and copepod counts (Huq et al., 2005). These factors may contribute to the seasonality and secular trends seen in cholera outbreaks. In Dhaka Lobitz et al (2000) were the first to observe that both sea surface temperature and sea surface height are correlated with temporal fluctuations of cholera. In Ghana, de Magny et al (2007) observed a coherence between cholera outbreak resurgences and climatic/environmental parameters such as rainfall, Southern Oscillation Index and Land Surface Temperature.

4. Spatial epidemiology and cholera

The analysis of the spatial distribution of disease incidence and its relationship to potential risk factors (referred to in general in this paper as spatial epidemiology) has an important role to play in various kinds of public health and epidemiological studies. Recent advancements in technology and the increasingly powerful and versatile spatial statistical tools developed
in this application area are capable of addressing more complex health issues than was hitherto the case. The field of spatial statistics involves the statistical analysis of observations with associated geographical location. Often these observations are not Gaussian distribution and are not independent (two main-stays in the development of statistical methods). Fortunately, a wide variety of statistical techniques for spatial epidemiologic inference have developed in recent years, coalescing into a collection of approaches which address specific questions. Consequently, the field of spatial epidemiology has been a subject of several lengthy texts (Elliott et al., 2000, Lawson, 2001, Waller and Gotway, 2004). Yet, few authors have addressed the spatial epidemiology of cholera (Ali et al, 2002a, 2002b; Ali et al., 2006; Borroto and Martinez-Piedra, 2000). Following Elliot et al (2000) and Lawson (2001), spatial epidemiology generically comprises at least three types of study focus: These are (1) disease mapping, (2) disease clustering and (3) ecological analysis (geographical correlation analysis). In this regard, we discuss methodological significance of disease mapping, disease clustering and ecological analysis with special emphasis on their applications in cholera studies.

4.1 Disease mapping and cholera

Disease maps have played a key descriptive role in spatial epidemiology. Disease maps are useful in suggesting hypotheses for further investigation or as part of general health surveillance and the monitoring of health problems. A famous historical example is the classical epidemiological work of John Snow. Mapping the locations of cholera victims, Snow was able to trace the cause of the disease to a contaminated water source. Surprisingly, this was done 20 years before Koch and Pasteur established the beginnings of microbiology (Koch, 1884). Disease mapping has long been in the form of plotting the observed disease cases or prevalence. Borroto and Martinez-Piedra (2000) used Geographic Information System (GIS) to map cumulative incidence rates of cholera in 32 Mexican states. Chevallier et al (2004) used cartographic representation of cholera incidence rates to study the spatial distribution of cholera in Ecuador. Raw disease rates yield less precise estimates for small populations and vice versa; hence, mapping the raw estimates of disease occurrence can lead to spurious spatial features. Thus, maps of raw disease incidences are not suitable for appropriate epidemiologic inferences. Bithel (2000), Diggle (2000), Lawson (2001), and Lawson and Clark (2002) provide recent reviews of current appropriate disease mapping methods. Several statistical smoothing techniques have been proposed to filter out the noise (rate variations) caused by population variability (e.g. median-based head-banging (Hansen, 1991), spatial filtering (Bithel, 1990; Rushton and Lolonis, 1996), empirical Bayes smoothing (Clayton and Kaldor, 1987), full Bayesian smoothing (Besag et al., 1991, 1995), and geostatistical methods (Oliver et al., 1998; Webster et al., 1994; Carrat and Valleron, 1992; Goovaerts, 2005; Goovaerts and Jacquez, 2004; Berke, 2004)). However, few have been applied in cholera studies. Kuo and Fukui (2007) have used the inverse distance weighted (IDW) interpolation technique to map the temporal features of cholera in the Fukushima prefecture Japan. Ali et al (2002) used kriging to interpolate and map the spatial risk of cholera in Bangladesh at regularly space interval. Ali et al (2006) presented the first application of Poisson kriging to the spatial interpolation of local cholera rates, resulting in continuous maps of cholera rate estimates and associated prediction variance.
4.2 Disease clustering and cholera

Fundamental to the spatial epidemiologist is the investigation of possible disease clusters. Cluster analysis provides opportunities for the epidemiologist to understand possible associations between demographic and environmental exposures and the spatial distribution of diseases (Besag and Newell, 1991; Kulldorff and Nagarwalla, 1995; Kulldorff et al., 1997). There are numerous methods for testing global clustering, including those methods proposed by Alt and Vach (1991), Besag and Newell (1991), Cuzick and Edwards (1990), Diggle and Chetwynd (1991), Grimson (1991), Moran (1950), Tango (1995, 1999, 2000), Walter (1992a, 1992b, 1993) and Whittemore et al (1987). Siddiqui et al (2006) applied Cuzick-Edward’s k-Nearest Neighbors test (Cuzick and Edwards, 1990) to evaluate clustering of cholera cases in Pakistan. Using the Moran’s Index, Borroto and Martinez-Piedra (2000) have described the spatial distribution of cholera in Mexican states as clustered. This clustering reflects a north-south gradient and spatial clustering of southern states with higher incidence and spatial clustering of northern states with low incidence. Likewise, the Moran’s Index has been used to evaluate the clustering of cholera in the Lusaka area of Zambia (Sasaki et al., 2008) and in Madras (India) (Ruiz-Moreno et al., 2007). Osei et al (2008) have also used the Moran’s Index to evaluate global clustering of cholera in the Ashanti Region of Ghana. However, global cluster analysis ran the risk of obscuring local effects since the assumption of stationarity is rarely met. Locating and/or defining the characteristics of disease clusters, i.e. local cluster analysis, can inform hypothesis of population or environmental drivers of ill-health, as well as direct the prevention or treatment efforts of health care workers. Using the popular spatial statistics approach, i.e. Ripley’s K index, Ruiz-Moreno et al (2007) observed that clustering of cholera in Bangladesh occur at different spatial scales. Local clustering methods such as the Circular Scan Statistic (Kulldorff, 1997) and the Flexible Scan Statistic (Tango and Takahashi, 2005) have been used to detect and map the clustering of cholera in the city of Kumasi-Ghana (Osei et al., 2010; 2011). They emphasize that the Circular Scan Statistic can underestimate the relative risk of cholera clusters compared with the Flexible Scan Statistic. Emch and Ali (2003) have also used the spatial scan statistic to evaluate clustering of cholera.

4.3 Ecological analysis and cholera

A significant interest in spatial epidemiology also lies in identifying associated risk factors which enhance the risk of infection, the so called ecological analysis (Lawson et al., 1999a, 1999b; Lawson, 2001) or geographic correlations studies (Elliott et al., 2000). Understanding the spatial relationship between cholera and ecological risk factors has always been a challenge. Most authors ignore the geographical structure (spatial autocorrelation) of the data in the statistical analysis. For instance, Ali et al (2001, 2002a, 2002b) have utilized logistic regression, simple and multiple regression models to study the spatial epidemiology of cholera in an endemic area of Bangladesh. In their study, spatial filtering methods (Talbot et al., 2000), typically spatial moving average (Kafadar, 1996), and traditional geostatistics were only used to remove noise and transform cholera and environmental data into a spatially continuous form. This notwithstanding, the effect of spatial proximity or geographical structure of the data was not incorporated in the statistical model. Sasaki et al (2008) investigated risk factors of cholera with a GIS and matched case-case control in a peri-urban area of Luzaka, Zambia. Although a spatial autocorrelation analysis using Moran’s Index
was found to be statistically significant, this was never incorporated in the logistic and multiple regression models. Other authors have also used classical statistical methods to analyze the risk factors of cholera. Sasaki et al (2008) applied logistic and multiple regression models to examine risk factors of cholera in a peri-urban area of Luzaka, Zambia. Mugoya et al (2005) used logistic regression analysis to investigate the spread of cholera in Kenya. Ackers et al (1998) used Pearson correlation coefficient to determine the correlation between cholera incidence rates and socioeconomic and environmental risk factors in Latin America. Kuo and Fukui (2007) used a logarithmic regression to model the diffusion of cholera in Japan. De Magny et al (2008) used a Poisson regression to model environmental variables associated with cholera in Bangladesh.

Geographical data are correlated in space; therefore, data in close geographical proximity is more likely to be influenced by similar ecological factors and therefore affected in a similar way, i.e. spatial autocorrelation. Consequently, when these standard statistical methods are used to analyze geographically correlated data, the standard error of the covariate parameters is underestimated and thus the statistical significance is overestimated (Cressie, 1993). Yet, few studies have incorporated the effect of geographical proximity in cholera studies (Ali et al., 2002a, 2002b, 2006; Borroto and Martinez-Piedra, 2000). Spatial statistical methods, such as spatial regression models, incorporate spatial autocorrelation according to the way geographical neighbors are defined. Osei and Duker (2008) have used spatial regression models (both spatial lag and spatial error models) to explore the spatial dependency of cholera prevalence on an important local environmental factor (open-space refuse dumps) in Kumasi, Ghana. Inhabitants with high density of refuse dumps were observed to have higher cholera prevalence than those with lower density of refuse dumps (Osei and Duker, 2008). Moreover, inhabitants close to refuse dumps were observed to have higher cholera prevalence than those farther. Similarly, Osei et al (2010) have used spatial regression models to explore the spatial dependency of cholera on potential contaminated water bodies.

5. Conclusion

Cholera has been a public health burden for ages. Unlike the biological characteristics, relatively little effort has been made to understand the spatial epidemiology. Understanding the spatial patterns is useful for effective health planning and resource allocation. This review emphasized on the generic and spatial epidemiology of cholera. Important spatial epidemiologic tools applied in cholera studies have also been discussed in this review. However, not all the knowledge of cholera epidemiology has been captured in this review. Further studies are required to fully explain the spatial epidemiology of cholera.

6. References


Cholera


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Cholera and Spatial Epidemiology


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Cholera, a problem in Third World countries, is a complicated diarrheal disease caused by the bacterium Vibrio cholerae. The latest outbreak in Haiti and surrounding areas in 2010 illustrated that cholera remains a serious threat to public health and safety. With advancements in research, cholera can be prevented and effectively treated. Irrespective of "Military" or "Monetary" power, with one's "Own Power", we can defeat this disease. The book "Cholera" is a valuable resource of power (knowledge) not only for cholera researchers but for anyone interested in promoting the health of people. Experts from different parts of the world have contributed to this important work thereby generating this power. Key features include the history of cholera, geographical distribution of the disease, mode of transmission, Vibrio cholerae activities, characterization of cholera toxin, cholera antagonists and preventive measures.

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