Review

Cholera and climate: revisiting the quantitative evidence

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Abstract

Cholera dynamics in endemic regions display regular seasonal cycles and pronounced interannual variability. We review here the current quantitative evidence for the influence of climate on cholera dynamics with reference to the early literature on the subject. We also briefly review the incipient status of mathematical models for cholera and argue that these models are important for understanding climatic influences in the context of the population dynamics of the disease. A better understanding of disease risk related to the environment should further underscore the need for changing the socioeconomic conditions conducive to cholera. © 2002 Éditions scientifiques et médicales Elsevier SAS. All rights reserved.

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Records afford evidence of an undoubted relation between the meteorology of a place and its liability to cholera activity

—*H.W. Bellew (1884)*

1. Introduction

Growing concerns over the effects of climate change and environmental deterioration are driving current interest in the influence of climate on disease dynamics. The importance of climatic factors, however, is controversial because of the many human and socioeconomic determinants [1], even for vector-borne diseases such as malaria with well-established relations between weather and transmission capacity. Climate and disease associations in the past have lacked quantitative support, certainly for cholera and other diseases with less consensus on environmental drivers. The unprecedented and growing availability of climate data from remote sensing and reanalysis, as well as developments in the forecasting of climate variability, present new opportunities for retrospective analysis and epidemic forecasting. For cholera, recent studies have begun to take advantage of existing time series on the dynamics of the disease [2–4]. Here we assess the evidence from a quantitative perspective. In doing so, we bridge early and recent literature on climatic drivers of cholera from two disconnected periods of intense interest on the subject.

The search for climatic and environmental explanations of cholera began over 100 years ago in former Bengal and other regions of the Indian subcontinent. Evidence supporting the autochtonous nature of *Vibrio cholerae* in brackish waters and estuaries (e.g. [5]) has more recently highlighted the potential significance of environmental factors to the dynamics of the disease. Interestingly, the debate on the role of climate has for cholera an early precedent in the dispute opposing the so-called 'localists', who emphasized geography and environment, and the 'contagionists', who instead invoked man and sanitary conditions for the propagation of infection [6]. One century later, the importance of sanitary conditions is clearly indisputable: the infrastructure providing safe water and sewage treatment in industrialized nations has made the sustained transmission of cholera extremely unlikely [7]. Nonetheless, cholera remains a public health problem in large regions of the globe. Currently reported in over 70 countries, the disease is now in its seventh pandemic, which began in 1961 in Indonesia and has spread through Asia, Africa, and more recently Latin America.

The mechanistic basis for a climate–cholera connection, which is likely to involve multiple pathways, remains poorly understood. The marked seasonality of cholera and the often quoted simultaneous appearance of cases at different locations [8,9] have been main reasons for the long-standing search for climatic and environmental drivers. They have led to the view that primary transmission from an environmental reservoir initiates the seasonal outbreaks of cholera in endemic regions [9]. In this view, climatic factors such as water temperature would drive seasonality through their direct influence on the abundance and/or toxicity of *V. cholerae* in the environment, or alternatively, through their indirect influence on other aquatic organisms such as zooplankton, phytoplankton and macrophytes, to which the pathogen is found to attach [10,11]. Advances in methods to sample the bacterium quantitatively in the environment are beginning to address this hypothesis, by linking environmental factors, bacterial counts and cholera cases (e.g. [10,12]). Climatic variables related to water levels such as rainfall have also been invoked to explain cholera patterns since early times. Floods and droughts can affect not only the concentration of the bacterium in the environment, but its survival through the effect of salinity [13], pH or nutrient concentrations, as well as human exposure to the pathogen, sanitary conditions and susceptibility to disease. Unraveling the causal pathways linking climate to disease prevalence will require additional knowledge on the ecology of the pathogen. We do not attempt to review here the evidence for the proposed mechanisms of climate–cholera connections or for the related subject of an environmental reservoir, both of which have been covered extensively elsewhere (e.g. [10,14]).

We address instead at the opposite but complementary end of the spectrum, the quantitative evidence for a climate–cholera connection from the perspective of data analysis. This connection includes the role of climate not only in the seasonality of the disease but also in its interannual variability, which can be pronounced. We further restrict the scope of this review to the endemic dynamics of cholera, which best allow the study of climate forcing through time series analysis. We describe briefly the incipient status of mathematical models for cholera and illustrate their potential application to the understanding of environmental forcing in the context of disease dynamics. Our main goal is to identify open areas requiring further quantitative analysis, not only to better understand and support associations with climate but also to ultimately predict responses to it. We begin with a brief section on early observations on cholera's spatial distribution from the 'localist' perspective, which sets the stage for climate as a driver of temporal patterns of disease.

The final section on mathematical models of cholera brings us back full circle to argue that these models are essential to integrate the 'localist' and 'contagionist' views.
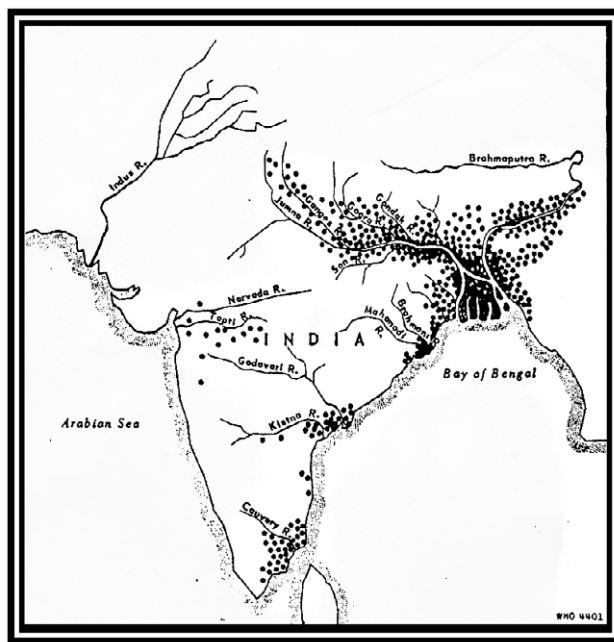

Fig. 1. Historical distribution of endemic cholera in South Asia. The level of endemicity (calculated as the average incidence during the 15 healthiest years between 1901 and 1945) is shown by the variation in the density of dots (from [17]).

2. The geography of cholera

The delta region of the Ganges and the Bramaputra has long been identified as cholera's 'native habitat' [15] and a source for the periodic pandemic spread of the disease. Smaller estuaries, such as those of the Madras province, were also recognized as endemic centers [16] (Fig. 1). Despite similar population densities and sanitary conditions, other deltas in South-East Asia did not (and do not) maintain cholera transmission (e.g. [17], Fig. 1), indicating that other local determinants are critical for cholera's maintenance.

During the pandemics several spatial characteristics were noted. The coldest inhabited regions were spared from the disease and the typical summer epidemics at high latitudes suggested temperature restrictions for the pathogen. Also higher altitudes appeared to be at reduced risk. The London epidemic, famous for the discovery by Snow of cholera's connection to water, provided a less well-known example of the spatial relation of the disease with altitude above the river Thames [15,18]. Cholera's predisposition to follow river basins was explained in the 19th century by patterns of water accumulation which are inversely related to altitude and to the water retaining qualities of soil [15]. Moist and humid conditions have also long been associated with cholera's spatial distribution. For example, cholera's incidence in nine provinces of former British India increases with average annual rainfall as illustrated in Fig. 2.

The extensive studies in the 19th century relating the propagation of cholera in Europe with soil type, may reflect not only the water-absorbing qualities stressed by Hirsch [15] but also the soil-dependent pH of surface waters. The
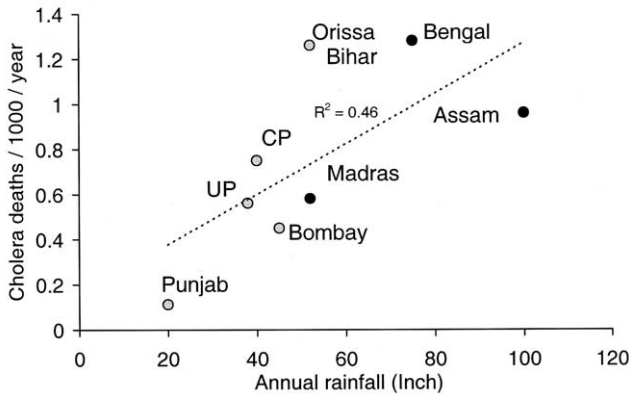
Fig. 2. Average annual mortality per 1000 of population in provinces of former British India between 1920 and 1939 and average annual rainfall in the same period based on data from [21]. Provinces with a single seasonal peak (open circles) and provinces with two annual peaks (black circles) are shown.
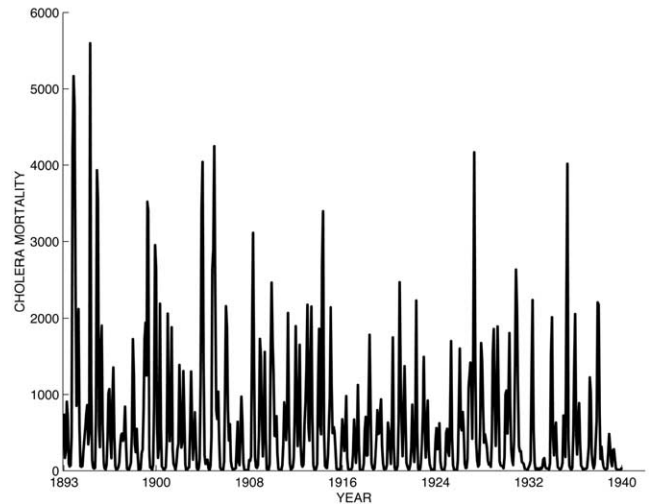

Fig. 3. Monthly cholera deaths in the Dhaka district between 1893 and 1940 from historical records for former British India (from [35]). The typical seasonal pattern with two peaks per year is modulated by longer cycles with considerable variation in total deaths from year to year.

cholera-free interior of tropical rain forests in South America with acidic surface water supports the significance of pH in the spatial distribution of the disease. Many of these historical observations can be related to physical and chemical niche requirements of *V. cholerae* now identified under controlled laboratory conditions (e.g. [19–20]).

3. Interannual variability

Cholera appears to wax and wane in endemic regions on time scales from 3 to 6 years, a pattern that has long been recognized (Fig. 3). Bellew [21] identified 3-year cycles with data from several provinces and for India as a whole between 1862 and 1881, with years of drought and famine as times of peak incidence. Russell [22,23], who applied a formal spectral analysis remarkable for the times, identified at the district level dominant frequencies of 5–6 years in Bengal.

Early explanations for these cycles were already linked to climate. In 1923, the director of public health in Bengal related in his yearly report the 'cyclical periodicity' of cholera to the cycles of rainfall. Periods of deficient rainfall were associated with exacerbations of cholera and explained by observations of epidemics under famine conditions [21,24–25]. Deficient monsoon rainfall was shown to precede 40 out of 41 epidemics of cholera over a period of 45 years in 45 divisions of British India [16]. Limited and impure water supplies during periods of drought were proposed as the link between climate and disease [16]. Another mechanism linking drought to cholera exacerbations was proposed much more recently by Drasar [26] who invoked changes in the virulence of the pathogen. By analogy with other bacteria, the mutation rate of *V. cholerae* would increase under malnutrition of the human host. The proposed effect of drought on cholera appears to contradict the positive association described earlier for different geo-

graphic regions and annual average rainfall (Fig. 2). However, as we explain later in the context of seasonality, the effect of rainfall's temporal variability depends on mean rainfall levels and differs between dry and wet regions.

Interestingly, concomitant with early studies of cholera and droughts, rainfall patterns in India were being investigated by Sir Gilbert Walker [27], the father of the El Niño Southern Oscillation (ENSO). The current hypothesis of a connection between El Niño and cholera originated, however, from an observation in another part of the world, the coast of Peru, where cholera initiated with explosive epidemics its spread through South America after being absent for almost 100 years [10,28]. The timing of these epidemics was noted to coincide with the El Niño event of 1991–1992. Such events are characterized by the anomalous warming of sea surface temperatures (SSTs) in a large area of the tropical Pacific including the coast of Peru. This raised the possibility that water temperatures through a direct or indirect effect on the pathogen influenced the risk of infection [10].

The above observations suggested an influence of ENSO but relied on observations for a single El Niño event. Because ENSO fluctuates with a dominant period of approximately 4 years, long time series are required to examine quantitatively whether it influences cholera. The historical data for Bengal and the time series from on-going surveillance programs by the International Center for Diarrheal Disease Research, Bangladesh (ICDDR,B) provide some of the longest records available and therefore are a natural place to begin. Bouma and Pascual [4] showed a significant correlation between cholera mortality in the spring season for Bengal and an El Niño index given by SST anomalies in a region of the subtropical Pacific (Table 1). Further evidence was found with a more recent data set from an on-going surveillance program by the ICDDR,B in

Table 1
Interannual cholera variability

Climate variable	Reference (location, time)	Type of study
ENSO: SST anomalies in the Pacific	Epstein et al. (1993) (coast of Peru, 1991–1992)	QO
	Colwell (1996) (coast of Peru, 1991–1992)	QO
	Pascual et al. (2000) (Bangladesh, 1980–1998)	46% SSA and spectral analysis 67% nonlinear time series models [a]
	Bouma and Pascual (2001) (Bengal, 1881–1940)	41% linear correlation
Sea surface temperature–ambient temperature	Colwell (1996) (Bangladesh, 1994)	QO
	Lobitz et al. (2000) (Bangladesh, 1992–1995)	QO
	Bouma and Pascual (2001) (Bengal, 1881–1940)	25% linear correlation
	Speelmon et al. (2000) (Lima, Peru, 1997–1999)	24% linear correlation
Sea surface height	Lobitz et al. (2000) (Bangladesh, 1992–1995)	QO

Summary of climate–disease links. The type of study refers to qualitative observations (QO) or quantitative analyses. Qualitative observations include descriptions of coincident patterns of variation and/or studies of single year events. For quantitative studies, the method and the percent of the variance accounted for are given.

[a] Includes previous disease levels and ENSO. It was not possible to ascribe a specific percentage of the variance to ENSO separately because the effect of the different independent variables was not additive in this nonlinear model.

Dhaka, Bangladesh [3]. In this program, a systematic subsample of all patients visiting the hospital, which serves as the main treatment center for the greater Dhaka city area, is tested for cholera. The resulting time series of percent cholera cases between 1980 and 1998 shows a dominant period in the interannual variability of cholera of 3.7 years, which coincides exactly with that obtained for an ENSO index known as Niño3.4 given by SST anomalies in a region of the equatorial Pacific [3]. Singular spectral analysis, a statistical method allowing the decomposition of the time series into principal components, showed that this frequency accounts for 46% of the variance in the interannual variability of cholera [3]. The association with ENSO was further supported by a nonlinear time series approach that incorporated as independent variables not only ENSO but previous disease levels. The latter were used as surrogates for variables related to the intrinsic dynamics of the disease such as the susceptible fraction of the population. The selected model incorporated both variables and identified a lag of 11 months between ENSO and cholera [3]. This so-called teleconnection or connection at a distance between cholera in Bangladesh and SST anomalies in the Pacific was further supported by results addressing regional climate variability (Fig. 4 in [3]). These results only begin, however, to close the link to disease, which brings us to the postulated effect of local water temperatures [10].

Water temperatures are known to influence the presence and abundance of the pathogen in rivers of coastal Peru [12]. Warmer air temperatures have also been associated with an increase in cases of diarrhoeal diseases in children in Lima, Peru [29,30] and are positively correlated with the monthly number of cholera cases for a period of 3 years including the El Niño event of 1998 [31]. SSTs in coastal

regions have been proposed as a major factor driving cholera outbreaks [2,10,28]. Recent observations on this link for the Bay of Bengal have relied, however, on coincident patterns of seasonal variation and do not directly address interannual variability. For the historical data, Bouma and Pascual [4] report a significant linear correlation between coastal SSTs in the Bay of Bengal and the intensity of cholera's spring peak in the historical data (Table 1). The correlation is weaker, however, than that obtained for remote SSTs in the Pacific and varies substantially with location, being more consistently significant for coastal districts.

In summary, recent data analyses support a temporal association between ENSO and cholera's interannual variability in Bangladesh and former Bengal. The causal pathway(s) explaining this teleconnection, including the regional climate variables that mediate it in South Asia, require further investigation. Existing evidence favours a role of increased water temperature and ecological change through changes in the survival and growth of the pathogen. A role of ENSO via water temperatures is further supported by recent studies of cholera in Peru. Early studies for the Indian subcontinent suggest another climate driver in the form of droughts. Given the importance of the monsoons in the climate of South Asia, their influence on cholera deserves to be revisited and examined with modern quantitative approaches for both recent and historical disease data.

Causal pathways, however, need not be unique and other influences on cholera dynamics are currently under investigation. These influences include sea surface height (SSH) [2] and river discharge, climate variables that affect water levels and salinity. In fact, the tracking of the propagation of cholera-related signals in regional temperatures suggests a
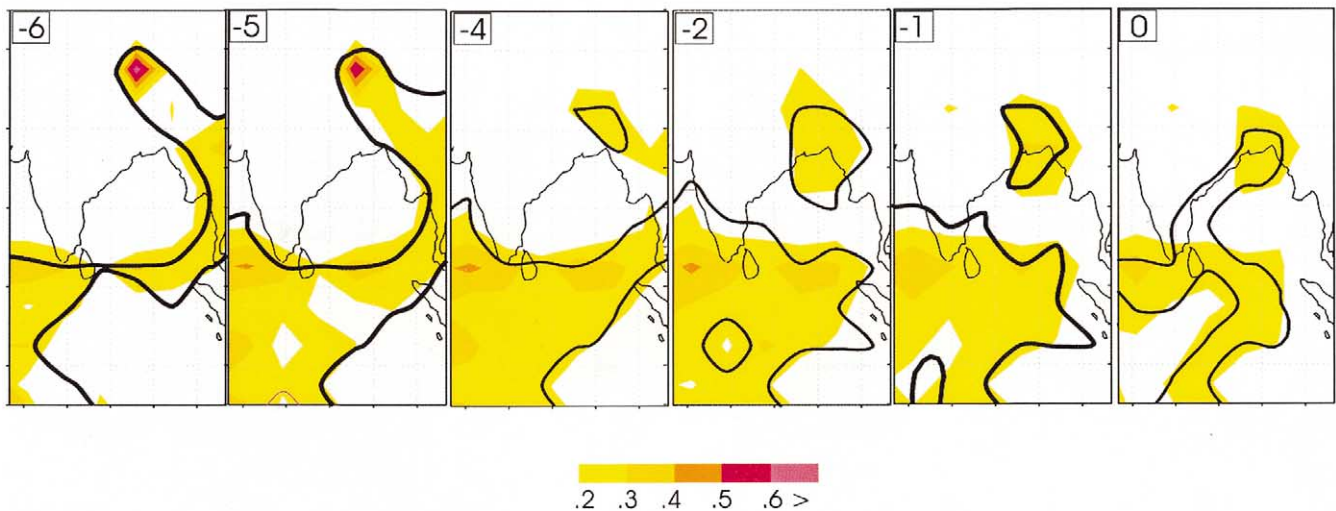
Fig. 4. Maps of correlation coefficients between cholera in Dhaka and temperatures on land and at sea for different lags, with the environmental variable anticipating disease (monthly data from 1980 to 1995). Monthly disease data are percentage cholera cases obtained by the ICDDR,B in Dhaka, Bangladesh, from a systematic sample of the patients visiting the facility. Monthly temperature data were extracted from the Global Ocean Surface Temperature Atlas (GOSTAplus) for a grid of 5° latitude and longitude. GOSTAplus was provided by the NASA Physical Oceanography Distributed Active Archive Center at the Jet Propulsion Laboratory/California Institute of Technology. Black boundaries indicate regions where the correlations are significant at the 0.002 level. (For each point on the map, the significance was calculated with a Monte Carlo test by randomly rearranging the elements of each time series at all points in 999 permutations.) A positive association between cholera and temperature is first observed to the north of Bangladesh over the Himalayas, where temperature leads cholera increases by 6 months. The pattern then moves south, though it weakens, as the lag to cholera decreases (from [3], copyright Science).

potential role of inland areas in Bangladesh in anticipating the coast (Fig. 4, [3]). This observation raises new questions about the relative roles that regional factors may play in the interannual variability of cholera. Intermediate factors might include river-mediated parameters influenced by snow melt in the Himalayas, such as river discharge and salinity, and/or interactions with local weather patterns, such as changes in monsoonal rains.

Table 1 summarizes the described climatic influences on the interannual variability of cholera and the type of evidence supporting these. It is apparent that more quantitative studies of long records are needed, as well as more emphasis on determining the strength of the climatic influences. Furthermore, the role of climate needs to be considered in the context of other (non-climatic) potential drivers of disease, such as those related to population structure and strain variation. Changes in birth rates fuel the younger age classes more susceptible to disease. The lack of host immunity against a new strain also leads to a larger number of susceptible individuals in the population and to a larger number of cases among the age classes that are typically more resistant to the disease [32]. Scientists have speculated about the pandemics being caused by different biotypes of cholera. Two out of the last three pandemics that occurred after the bacterium was first isolated were caused by different biotypes, thus providing an explanation for the global excursions of the pathogen from its endemic homeland. Recent cycles in the dominance of different strains are beginning to be documented but their consequences for disease dynamics remain to be examined (e.g. Fig. 11.3 in [33]).

4. Seasonality

The seasonality of cholera exhibits remarkable regularity but varies geographically. This geographic variation in endemic and peripheral, more epidemic, regions alike has been described as "the most striking peculiarity in the deportment of disease in India" [21]. This appeared to still be the case when over a century later Feachem [34] wrote: "these different seasonal patterns... are such a dominant feature of cholera epidemiology, and in such contrast to other bacterial diarrhoeas which peak during the monsoon in mid-summer, that their explanation probably holds the key to fundamental insights into cholera transmission, ecology, and control".

For the Indian subcontinent two main seasonal patterns have been described. Endemic estuarine regions and surroundings such as most of Bengal and parts of the province of Madras, exhibited typically two annual cholera seasons with a marked depression during the main monsoon. In other parts of the subcontinent, particularly the dryer provinces including Bihar, Orissa, Punjab, and Assam, cholera peaked during the monsoon. The Sanitary Commission for Bengal [35] reported this anomaly: "cholera does not prevail in the highlands until the rains have well set in, while the contrary is the case with respect to the lowlands". Although in some dry regions the seasonal increase precedes the rains, precipitation does not appear to suppress the annual rise. The bimodal cycle is the one typically described in the more recent literature for the classical biotype of *V. cholerae* in Bangladesh, although the dominant peak has shifted to the fall with the appearance of the El Tor biotype
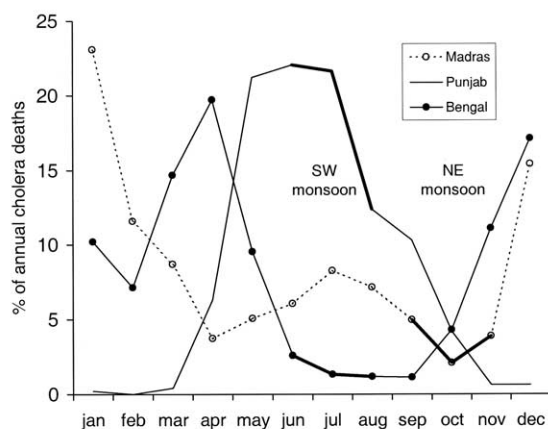
Fig. 5. Variability of seasonal cholera in the high endemic provinces Bengal and Madras (bimodal pattern) and in the epidemic Punjab province (single peak). Bold lines show the main rainfall season with the South West monsoon in Bengal and Punjab, and the North East monsoon dominating Madras. Data from [16].

(e.g. [8]). In Latin America and Africa a single peak per year is typically found [12,30,36].

The decrease in cholera during the monsoon can be explained, as has been attempted for Calcutta and 19th century London, by a reduction in salinity levels of surface waters presumably below the optimum requirements of the pathogen as the result of increased river discharge into the estuarine system [19]. Rainfall can also reduce cholera cases by diluting the concentration of the pathogen in aquatic environments during the monsoon season. The hypothesis that seasonal monsoon rains reduce cholera transmission was confounded by the existence of the completely opposite pattern in regions where a single annual peak in cholera mortality occurred during the monsoon season. However, this monsoon-associated pattern was found in the dryer parts of former British India, indicating that overall water levels matter and appear to determine whether the effect of rainfall is positive or negative. In dry regions where the rainfall and cholera seasons coincide, the availability of water in the environment would act as a limiting factor for the transmission of the disease (Fig. 5).

Floods and droughts have been related to the seasonality of cholera in other parts of the world. The Central Amazon region is characterized by seasonal flooding of the Negro and Amazon Rivers, driven mainly by snow melt in Andean headwaters [36]. It was noted that cholera outbreaks from 1992 to 1995 started during the dry season, peaked at the beginning of the rising waters, and declined during the high water period [36].

Temperature in aquatic reservoirs, particularly SST in coastal regions, has recently attracted considerable attention as a remote sensing variable that could provide a predictor of cholera [2,10]. In particular, SSTs in the Bay of Bengal were noted to exhibit a bimodal pattern similar to that of cholera with two peaks per year. From visual inspection of these patterns, however, it is unclear whether there is a

consistent lag between disease prevalence and SST across years and across seasons (spring and fall–winter). For the historical records, spring mortality in Bengal shows significant correlations with SST, particularly in coastal regions, while for the winter peak, dominant further away from the estuary, the association appears less consistent [4]. In all provinces, except lowest latitude Madras, cholera shows a decline in January and February which may be temperature related. For a more recent cholera time series (1966–1980) from Matlab, Bangladesh, Glass et al. [8] noted the coincident timing of the main cholera season in the fall with the highest temperatures, based on the mean seasonal pattern from 1973–1980 when the El Tor biotype was dominant. Furthermore, the end of the season coincided with the cold winter temperatures. They mentioned, however, the failure to forecast the yearly time of onset of the fall–winter outbreak for both the classical and the El Tor periods based on changes in environmental parameters, including temperature.

For Peru, Franco et al. [12] provided evidence for a positive association between counts of the pathogen V. cholerae, measured with a probe for the cholera toxin (CT) gene, and river water temperature 2 months earlier. The influence of temperature on the timing of the pathogen's appearance was demonstrated using logistic regression analysis, with the presence or absence of CT-positive V. cholerae as dependent variable. In addition, the number of cholera cases correlated significantly with CT-positive cholera counts at 'cleaner' sites upriver 2–3 months earlier, with r values as high as 0.72 [12].

In summary, observations support a role of water temperature in the seasonality of cholera in Peru and in parts of the bimodal cycle in the Indian subcontinent, namely in the initiation of the spring peak and the decrease of the fall–winter peak. The climatic driver of the fall–winter increase, which leads typically to the largest annual outbreak, appears less clear. The effect of monsoon precipitation in cholera's summer decrease varies between high and low regions and appears relative to overall water levels. However, quantitative studies of climate influences on the seasonality of the disease are few. Thus, it is not yet possible to asses the strength of particular climatic drivers and the ability to forecast the timing of the seasonal outbreaks based on particular environmental factors.

A variable that deserves further study is river discharge and its impact on cholera through modifications of water levels, salinity, and pH. The spring decline in Calcutta starts with the increased river discharge following the snow melt in the Himalayas just before the monsoon period (Bouma, unpublished). The pH of the Ganges and the Bramaputra and related surface waters turns from alkaline to acidic with the onset of the swelling rivers in spring, returning to alkaline conditions before cholera's post-monsoon peak. Thus, the seasonality of pH in surface waters of Bengal appears to match well that of cholera (Bouma, unpublished) and is consistent with the combination of lower salinity and

decreased pH providing unfavourable conditions for the pathogen.

5. Mathematical models

Mathematical models of disease dynamics are central to a better understanding of responses to environmental forcing. A limited number of models have been published that explicitly deal with the dynamics of cholera [36–38]. The first of these was developed by Capasso [37] to describe the dynamics of the 1973 epidemic of cholera in Italy. It consisted of two equations to follow the dynamics of infected individuals and number of free-living infective stages (or fomites). More recently Codeço [36] developed a more general model of cholera with an additional equation for the susceptible fraction in the host population. We further generalize Codeço's model and include a fourth equation that describes the volume of water in which the fomites live. This allows us to explicitly consider changes in the volume of water that alter the concentration of infective stages and thus modify the force of infection experienced by susceptible hosts.

In a later publication we will explore the consequences of low levels of infection inducing immunological resistance in a proportion of the host population. Immunological resistance may also develop in infected individuals who recover from infection. In both cases resistance is transient and exposed individuals will eventually re-enter the pool of susceptibles.

The model can be described by the following set of four coupled differential equations for the susceptibles, S, infecteds, I, fomites (or bacterial abundance), F, and water volume, W:

$$\frac{dS}{dt} = (b - d)(H - S - I) + \rho I - \beta \frac{SF}{kW + F}$$

$$\frac{dI}{dt} = \beta \frac{SF}{kW + F} - (d + \rho + \alpha)I$$

$$\frac{dF}{dt} = (r - \mu)F + \lambda I$$

$$\frac{dW}{dt} = p + s - DW$$

The model parameters are described in Table 2. Notice that we have modified the saturating transmission function used by Codeço [36] to include the volume of water. In the absence of seasonal variation in river flow or precipitation, then water level will equilibrate at a level $W^* = (p + s)/D$ where p is the precipitation rate, s is stream flow, and d is the drainage rate. The force of infection experienced by any individual is given by:

$$f(S) = \frac{F}{F + kW^*}$$

Thus, force of infection is higher when water volumes are low, than when they are high (k is a constant that

Table 2
Parameters used in basic cholera model

b	Host per capita birth rate
d	Host per capita death rate from natural causes
β	Infection rate at which fomites cause infection in susceptible hosts
ρ	Recovery rate of infected individuals
k	Scaling constant that modifies water volume to determine number of fomites required to induce an infection in a susceptible
α	Increased mortality rate of infected hosts
r	Reproductive rate of free-living fomites (may be a function of temperature)
μ	Death rate of free-living infective stages
λ	Rate at which infecteds produce infective stages
p	Precipitation rate (may vary on an annual cycle)
s	River flow rate (may vary on an annual cycle)
D	Drainage rate of water downstream from site of infection per volume of water W

rescales water volume so that transmission occurs at 50% of its maximum rate at kW^*).

These equations can be used to derive an expression for the basic reproductive number of cholera, R_0, quantifying the number of new infections produced in a population of susceptibles by the first infected host individual. The value of R_0 and in particular whether it exceeds a threshold of 1, determines whether an outbreak develops or not. An approximate expression for R_0 may be obtained by arranging equations 1–4 above

$$R_0 \approx \frac{S\beta\lambda(r - \mu)}{kW^*\mu(d + \rho + \alpha)}$$

This expression illustrates the relative sensitivity of an outbreak of cholera to a number of key environmental variables. At least three of the parameters in the above equation can vary both annually and potentially on a longer climatic timescale: r and μ, the growth and mortality rates of the free-living stages of cholera; and W, the volume of water in which these free-living stages persist. While it is also possible that the rate at which humans contact water may vary seasonally, this will tend to occur in complicated ways that may depend on the age and sex of different individuals in the host population. Much of the current focus on climate–cholera connections has been on water temperature and on the consequences of its seasonal and interannual variation on the abundance of *V. cholerae* in the environment. The equation for R_0 clearly illustrates that cholera outbreaks in regions close to rivers, streams, and ponds will be in a constant tension between increasing temperatures, which tend to stimulate outbreaks, and increased water availability, which will tend to buffer outbreaks. Notice, however, that the dependence of R_0 on these two parameters differs and that R_0 is inversely proportional to W^*. Thus, R_0 may vary dramatically with climatic factors that alter directly the concentration of the pathogen rather than its growth. However, the effects of variations in bacterial growth rate and bacterial concentration will interact in time and with the number of susceptibles. Thus, the relative

timing of environmental fluctuations matters and should be investigated with mathematical models such as the one presented here. This will lead to a better understanding of responses to climatic drivers and help untangle the relative roles of proposed mechanisms. Although the full consequences of varying parameters will be explored elsewhere, this initial exercise already confirms that the relationship between cholera outbreaks and environmental variation is one that is both subtle and potentially complex when subject to different time lags that affect different parts of the system. Here it is important to note that we have simply examined models for cholera in regions adjacent to a permanent water resource (e.g. Bangladesh and Bengal). In regions where cholera is mainly transmitted from ephemeral seasonal water bodies a more complex model structure is required. Woolhouse et al. [39] have developed models for schistosomiasis whose structure could readily be adopted to examine cholera transmission in this more complicated case.

6. Conclusions

There is considerable evidence for a role of ENSO in the interannual variability of endemic cholera. Quantitative analyses of time series have so far concentrated on a small number of time series. It will be important to confirm these results and to quantify the strength of this climatic influence with other available data sets. The ability of statistical models to forecast interannual variability remains to be addressed. For Peru, analyses of longer time series should now be possible. For South Asia, further studies are needed of the regional variables that mediate the cholera–ENSO teleconnection locally. These will complement on-going research on the ecology of the pathogen as related to climate. Existing evidence favours a role of increased water temperature through its effect on the pathogen's growth and survival. However, factors affecting the quantity and quality of water in the environment, and thus the concentration of the pathogen, have not been sufficiently addressed. The role of the monsoons warrants further investigation.

Paradoxically, untangling the different potential causes of highly regular seasonal cycles appears more problematic since seasonality is itself the rule for most environmental variables of interest. We are therefore bound to find significant albeit weak correlations with approaches that average across seasons and years. The spatial variation of cholera's seasonality within a region provides invaluable additional information. The challenge is to account for these changes and to examine whether sufficiently strong associations can be found that allow prediction of the timing of outbreaks based on environmental variables. This will most likely require consideration of different drivers and/or lags for the different seasons in the case of the bimodal cycles. A complete explanation for these cycles remains elusive: evidence supports a role of water temperature in both the

spring rise and the winter decline, and a role of rainfall in the summer, whose sign depends on overall water availability; however, the second and main outbreak in the post-monsoon season requires further study.

By comparison to other infectious diseases, the mathematical modelling of cholera has only just begun. Mathematical models are important, however, to understand the role of climatic forcing in the context of disease dynamics, thereby integrating the separate early views of 'contagionists' and 'localists'. With a simple extension of a cholera model we have hinted here at the possibility that factors concentrating the pathogen in the environment, such as variations in water volume, can have dramatic effects on disease dynamics, perhaps more pronounced than those of factors affecting the pathogen's growth and survival. Along these lines, models can help us distinguish among different explanations for cholera's cycles, including those unrelated to climate and based on strain variation and population structure.

In closing a review about climate influences, it is nevertheless fitting to acknowledge the importance of socio-economic factors for cholera, described in current times as the "the disease of poverty" [40]. As socioeconomic conditions conducive to cholera persist in many countries, one goal often stated in studies of climatic/environmental influences is disease forecasting. Hopefully, an understanding of disease risk related to the environment can also underscore the need for improving these conditions.

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