EDE09-482
ORIGINAL ARTICLE

Title: Cholera in Bangladesh: Climatic components of seasonal variation

Authors:
Masahiro Hashizume[1]
Abu S.G. Faruque[2]
Yukiko Wagatsuma[3]
Taiichi Hayashi[4]
Ben Armstrong[5]

Authors' Institutions:
[1] Department of International Health, Institute of Tropical Medicine (NEKKEN) and the Global Center of Excellence program, Nagasaki University. Nagasaki,Japan
[2] International Centre for Diarrhoeal Disease Research, Bangladesh.
Mohakhali Dhaka, Bangladesh
[3] Department of Epidemiology, Graduate School of Comprehensive Human Sciences, University of Tsukuba.Tsukuba, Ibaraki, Japan
[4] Disaster Prevention Research Institute, Kyoto University.
Gokasho, Uji, Kyoto, Japan
[5] Public and Environmental Health Research Unit, London School of Hygiene and Tropical Medicine.London UK

Address for Correspondence:
Masahiro Hashizume
Department of International Health,
Institute of Tropical Medicine, Nagasaki University.
1-12-4, Sakamoto, Nagasaki 852-8523, Japan
tel/fax: (81) 95 819 7808
E-mail hashizum@nagasaki-u.ac.jp

Running head: Climatic components of seasonal variation in cholera

Source of financial support: Supported by ICDDR,B and Daiwa Foundation Small Grants.

Acknowledgements: ICDDR,B gratefully acknowledges the following donors who provide unrestricted support to the Centre's research efforts: Australian Agency for International Development (AusAID), Government of the People's Republic of Bangladesh, Canadian International Development Agency , Embassy of the Kingdom of the Netherlands, Swedish International Development Cooperation Agency, Swiss Agency for Development and Cooperation, and Department for International Development, UK.

Word count, abstract: 230
Word count, main text: 2701

No. Text pages: 19
No. Tables: 1

No. Figures: 2

Date submitted: 29 August 2009
Date accepted: 23 January 2010

ABSTRACT

Background: The mechanisms underlying the seasonality of cholera are still not fully understood, despite long-standing recognition of clear bimodal seasonality in Bangladesh. We aimed to quantify the contribution of climatic factors to seasonal variations in cholera incidence.

Methods: We investigated the association of seasonal and weather factors with the weekly number of cholera patients in Dhaka, Bangladesh, using Poisson regression models. The contribution of each weather factor (temperature and high and low rainfall) to seasonal variation was estimated as the mean over the study period (1983–2008) for each week of the year of each weather term. Fractions of the number of cholera patients attributed to each weather factor, assuming all values were constant at their minimum risk levels throughout the year, were estimated for spring and monsoon seasons separately.

Results: Lower temperature predicted a lower incidence of cholera in the first 15 weeks of the year. Low rainfall predicted a peak in spring, and high rainfall predicted a peak at the end of the monsoon. The risk predicted from all the weather factors combined showed a broadly bi-modal pattern, as observed in the raw data. Low rainfall explained

18% of the spring peak, and high rainfall explained 25% of the peak at the end of the monsoon.

Conclusions: Seasonal variation in temperature and rainfall contribute to cholera incidence in complex ways, presumably in interaction with unmeasured environmental or behavioral factors.

The mechanisms underlying the seasonality of cholera have not been fully elucidated, despite long-standing recognition of seasonal patterns. The incidence of cholera shows a bimodal seasonal distribution in Dhaka, Bangladesh: the first peak (April to May) occurs before the monsoon, and the second (September to October) occurs at the end of the monsoon, suggesting that weather factors could play a role.

Many studies have investigated the associations between weather and the incidence of cholera. Changes in rainfall, river level or ambient temperature have been suggested to play a role.[1-7] An earlier study in rural Bangladesh demonstrated an association of cholera cases with water temperature (with a lag of 6 weeks) and rainfall (with a lag of 8 weeks).[8] Rainfall can affect not only bacterial concentration in the environment, but also bacterial survival through the effects of salinity, pH or nutrient concentrations.[9] Rainfall could alter human exposure to the pathogen through changing sanitary conditions and also by affecting susceptibility to disease.[10] High rainfall may also wash away the vibriophages that prey on *Vibrio cholerae* in water, leading to cholera epidemics.[11] Sea surface temperature in the Bay of Bengal shows an annual bimodal cycle similar to the seasonal pattern of cholera in Bangladesh.[12] However, little epidemiologic research has formally investigated the extent to which cholera variation is explained by specific climatic factors. This issue is of interest both in its own right, and also for its potential to improve our understanding of host-pathogen ecology and our ability to predict epidemics. We aimed to quantify the extent to which climatic factors contribute to seasonal variation in the incidence of cholera. We also estimate the contribution of climatic factors to each peak of cholera incidence in Bangladesh.

METHODS

Data on the number of patients presenting with cholera each week were obtained from the International Centre for Diarrhoeal Disease Research, Bangladesh (ICDDR,B) Dhaka Hospital. This hospital serves a large population within the city of Dhaka and provides free treatment for more than 100,000 cases of diarrhoea each year. Every 25th patient has been enrolled in the surveillance system up to 1995 and every 50th patient since 1996. Stools from each patient were microbiologically examined to identify common enteric pathogens including vibrios. We retrieved information on the date of hospital visit and the pathogens identified from each stool specimen during a 26-year period (January 1983 to December 2008). A patient was classified as having cholera when *V. cholerae* O1 El Tor was identified in the stool specimen, regardless of the presence of other pathogens. We obtained daily rainfall and maximum temperature data in Dhaka from the Bangladesh Meteorological Department. The weekly mean maximum temperature and the total weekly rainfall were calculated from the daily records.

Statistical analysis

We investigated the association of seasonal and weather factors with the number of cholera patients per week at the Dhaka Hospital, using Poisson regression models allowing for overdispersion.[13] We modelled the effects of season, defined as annually-repeated patterns, using Fourier terms up to the sixth harmonic (a parameter for each 2 months), allowing between-year variations with indicator variables for the years of the study and weather variables. We also incorporated an indicator variable for the two periods with different sampling proportions (4% up to 1995 and 2% since 1996). We included seasonal as well as weather terms in the model despite seeking to explain the seasonal pattern because we did not wish to presume the importance of weather over other seasonal factors. We needed estimates of the effects of weather factors controlled for confounding by unmeasured seasonal effects.

The weather variables included temperature and high and low rainfall. Based on the models used in a previous study,[3] we defined “high rainfall” as rainfall averaged over lags 0−8 weeks above a threshold of 18 mm. Similarly, “low rainfall” was defined as rainfall averaged over lags 0−16 weeks below the same threshold. The temperature term was defined as the temperature averaged over lags 0−4 weeks below the cut-off of 31°C; the effect of temperature reached a plateau at this threshold (the 38th centile of the temperature distribution). These definitions were derived from plots of the smoothed relationships between weather factors (rainfall and temperature) and the number of cholera cases, suggesting log-linear associations above or below a threshold. We then fitted linear threshold models − i.e. models that assume a log-linear increase (or decrease) in risk above (or below) a threshold and no increase in risk below (or above) the threshold.[14] The choice of threshold was based on maximum likelihood estimation. By incorporating these linear terms of weather factors, the final model was as follows:

$$log[E(Y)] = \beta_{lowR}(low\_threshold\text{-}rain_{0-16})^{+} + \beta_{highR}(rain_{0-8},\text{-}high\_threshold)^{+} + \beta_{temp}(temp_{0-4}\text{-}threshold)^{-} + time(Fourier, 6\ harmonics/year) + i.year$$

The variables “rain” and “temp” indicate the mean weekly amount of rainfall and the average weekly temperature in each lag, respectively. “Fourier” represents trigonometric terms of annual periodicity and harmonics to the value stated. The term “i.year” represents indicator variables of year $(x)^+ = x$ if $x>0$, otherwise = 0. $(x)^- = x$ if $x<0$, otherwise = 0.

The contribution of each weather factor to seasonal variation was estimated as the mean over the years of the study, for each week of the year (1–52) of each weather term in the above model. For example, the mean of $\beta_{lowR}(low\_threshold\text{-}rain_{0-16})^+$ over the 26 years of the study provides an estimate of the contribution to seasonal variation of risks due to low rainfall. To show the effect of all weather factors combined, the sum of all weather terms was similarly averaged. The averages of model components were exponentiated for graphing to transform to the more interpretable relative-risk scale.

The percentage of cholera cases attributed to temperature, high rainfall and low rainfall was estimated using the methods of Bruzzi et al..[15] For rainfall, we took the baseline for relative risks (i.e., counterfactual temperature for attributable risk estimation) as the level at which the risk was minimum. For temperature, for which the minimum risk was at the lowest temperature and estimated imprecisely, the baseline level was taken as the 5th centile (25.2°C). For example, the attributable fraction (AF) for low rainfall in week i was calculated as follows;

$$AF_i \text{ (low rain)} = \{RR(r_L) - RR(0)\}/RR(r_L) = (\exp(\beta_L r_L) -1)/\exp(\beta_L r_L)$$

Overall attributable fraction was estimated as

$$AF = \{\Sigma Y_i AF_i\}/ \Sigma Y_i$$

Attributable fractions were estimated separately before (weeks 1–26) and after the monsoon (weeks 27–52) in addition to estimates for the whole year. The seasons are referred to as spring and monsoon. The sensitivity of the estimates to the complexity of the seasonal function (3 and 12 harmonics) was also examined. All statistical analyses were performed using Stata 10.0 software (Stata Corporation, College Station, Texas).

RESULTS

In total, 10,976 patients with El Tor cholera were identified in the surveillance system between 1983 and 2008. The mean (SD) weekly number of cholera patients was 8.1 (8.2). Seasonal variation in hospital visits due to cholera demonstrated the well-known bimodal seasonality, with a peak before the monsoon (spring peak) and at the end of the monsoon (monsoon peak), and a trough in the middle of the monsoon (Figure 1). This is similar to that reported in a previous study.[16]

Based on the model with all terms included, a high proportion of cholera cases (57%) were attributable to high temperature, while 17% were attributable to high rainfall and 8% were attributable to low rainfall (Table). The fractions attributed to high rainfall were higher in the monsoon (25%) than in the spring (8%). In contrast, the fractions attributed to low rainfall were higher in the spring (18%) than in the monsoon (<1%).

To show the extent to which the effects of weather on hospitalizations explained the seasonal pattern, Figure 2 presents the average annual pattern of relative risks predicted by each weather factor and their combination (Figure 2A), and the observed average seasonal pattern (Figure 2B). From the top graph, we see that: (1) because of the plateau of the temperature effect, the mean predicted relative risk remained constant throughout most of the year, but dropped below this in the first 15 weeks of the year; (2) the low rainfall effect predicted a peak at around week 10; (3) the high rainfall effect predicted a peak at around weeks 29–31. The risk predicted from all weather factors combined is broadly bi-modal, as in the raw data (bottom graph). However, the peak-trough ratio was much less in the predicted data than in the observed data (3.5 vs 6.5 in the spring and 3.6 vs 6.1 in the monsoon). Also, both peaks were predicted about 10 weeks earlier than they actually occurred.

The fractions attributed to weather factors changed little when the degree of seasonal control was halved (3 harmonics) or doubled (12 harmonics). The attributable fraction of temperature decreased only with 3 harmonics (from 57% to 51%). The annual pattern of relative risks predicted by each weather factor and their combination remained largely unchanged, although the predicted peak-trough ratio was reduced with half seasonal control (3.0 in the spring and 3.2 in the monsoon)

DISCUSSION

Although qualitative explanations of the environmental factors underlying seasonal occurrence of cholera are found in the literature, convincing quantitative evidence to support them has remained elusive. This study shows that meteorologic factors play some part in the seasonal variation in the number of cholera patients in Bangladesh, although interpretation of the results is not straightforward.

Our previous study looked at short-term associations of weather with cholera after controlling for seasonal and inter-annual patterns.[3] In contrast, this study has sought to explain the seasonal patterns of cholera. Our underlying paradigm is that the seasonality of cholera may be produced by both weather and by unmeasured environmental or behavioral factors. To do this we predicted the incidence of cholera in each week from direct effects of weather components estimated after controlling for unmeasured seasonal components. We then compared those predicted values with the real (observed) seasonality of cholera incidence to explore the contribution of weather parameters to overall seasonality.

The peak-trough ratio of the predicted data is substantially smaller than that of the observed data, both in the spring (3.5 vs 6.5) and in the monsoon (3.6 vs 6.1). This suggests that meteorologic factors determine part of the seasonal variation, but that other unmeasured environmental or behavioral factors that show regular seasonal cycles are responsible for the rest of the seasonal pattern. It is possible that our estimate of the part played by weather factors in seasonal variation was biased downwards as a result of imprecise modelling of the lag structure or functional form (shape) of their effects. Similarly, imprecise modelling of the lag structure of these effects could account for the earlier prediction of spring and monsoon peaks by our model. This discrepancy may be due to prolonged secondary infection through fecal-oral transmission, following primary transmission triggered by weather conditions. The weather conditions (dry and hot in the spring and wet and hot in the monsoon) presumably trigger primary transmission from a reservoir of *V. cholerae* in the aquatic environment. The secondary transmission, which is mediated by the ingestion of fecally contaminated water and food,[17] can be a major component of the epidemic and can continue for several weeks, irrespective of the initial weather conditions. The importance of secondary transmission is supported by recent time-series models fitted to the endemic dynamics of cholera in

Bangladesh.[5] A recent report based on molecular studies demonstrated outbreaks occurring in two communities in Bangladesh originating from local sources.[18]

Temperature was a strong risk factor in our data. Temperature could not explain the variation in cholera incidence between weeks 15 and 43, but could explain the winter trough. This is broadly consistent with the findings from an earlier study demonstrated that higher temperatures of surface water were associated with an increased number of cholera cases in rural Bangladesh.[8] Higher temperatures may promote the growth and multiplication of *V. cholerae*, which directly influences the toxicity of *V. cholerae* in aquatic environments.[9] Elevated pH levels in the aquatic environment as a result of increased aquatic plant or algal growth during periods of warm temperatures allow *V. cholerae* to outcompete other bacteria.[19] It has been suggested that the high correlation between sea surface temperature in the Bay of Bengal and outbreaks of cholera is due to warm water along the coast, coupled with plankton blooms driven by warm ocean temperatures, which provide favorable conditions for the multiplication of *V. cholerae*.[9,12]

Low rainfall can be expected to contribute to the first cholera peak, as low rainfall leads to changes in water supply and hygiene behaviors.[10] Some people in Dhaka rely on surface water for washing and bathing. This could increase the risk of contamination and exposure to cholera during periods of low rainfall, with more intensive use of available ponds and other surface water for washing and drinking.[9] Heavy rain during the monsoon leads to flooding, which may overtax water and sanitation systems and so promote the intake of contaminated water.[20] Ingestion of a few copepods carrying a high concentration of *V. cholerae* can initiate an infection.[21] This occurs more frequently when people are exposed to untreated water, such as occurs during flooding. The possible link between high rainfall and cholera may also be due to increased growth and multiplication of *V. cholerae*, as high rainfall increases the levels of insoluble iron, which improves the survival rate of *V. cholerae* in aquatic environments.[9] High rainfall may also wash away the vibriophages that prey on *V. cholerae* in the water, leading to cholera epidemics,[11] although a recent simulation study has not supported this hypothesis.[22]

Some previous studies in Matlab, rural Bangladesh, have not found any association between rainfall and the variability of cholera occurrence, despite the fact that Dhaka and Matlab show the same general bi-modal pattern of pre- and post-monsoon cholera increases.[4,16] An earlier study in rural Bangladesh reported a negative association between rainfall and the number of cholera cases.[8] The reasons for these differences are not clear, and are worth further investigation in other settings. A possible reason could be differences between urban Dhaka and rural areas in population density (crowding), hygiene and sanitation conditions or behavioral patterns. These factors might interact with exposure to contaminated water systems as a consequence of climatic conditions. Thus the association we observe between climatic factors and the seasonal pattern of cholera may be specific to low-lying urban areas with bodies of water that are vulnerable to flooding. The association may also depend on the degree of hygiene and sanitation in an area. The large estuary of Bangladesh provides an environmental reservoir for *V. cholerae* with topographic characteristics that may be unique to Bangladesh. Therefore, the findings of this study may not pertain to other places. Other weather variables (humidity, sunlight etc) could also affect cholera incidence.[4,9]

Improved understanding of the factors underlying the seasonality of infectious diseases can lead to the identification of environmental factors that might allow us to improve our ability to predict outbreaks, and contribute to improved control strategies, such as the development of climate-based early-warning systems.[23] In addition, identification of the specific environmental factors underlying seasonal occurrence of disease is a critical step towards predicting and understanding how global climate change might affect patterns of infectious diseases.[24,25] Nonetheless, the mechanisms underlying the seasonality of infectious diseases remain elusive, and there is a pressing need to develop methods to identify the causes of seasonality.[24-26] The methods used in this paper could be of use in such studies. Expected increases in temperature, changes in precipitation patterns, and increased flooding due to climate change in Bangladesh[27]could have a major impact on the seasonal pattern of cholera. Although the short-term associations reported here cannot be directly extrapolated to changes in climate over decades, they do provide a starting point for estimating the impact of climate change.

In summary, seasonal variation in the number of cholera patients in Bangladesh can be explained in part by temperature and rainfall. Low rainfall may contribute to the first peak in spring, and high rainfall to the second peak at the end of the monsoon, while low temperature may explain the winter trough. The methods used in this paper may be more widely applicable to the study of factors underlying the seasonality of infectious diseases.

REFERENCES

1. Bouma M, Pascual M. Seasonal and interannual cycles of endemic cholera in Bengal 1891-1940 in relation to climate and geography. *Hydrobiologia* 2001;**460**:147-156.
2. Colwell RR. Global climate and infectious disease: the cholera paradigm. *Science* 1996;**274**:2025-2031.
3. Hashizume M, Armstrong B, Hajat S, et al. The effect of rainfall on the incidence of cholera in Bangladesh. *Epidemiology* 2008;**19**:103-110.
4. Islam MS, Sharker MA, Rheman S, et al. Effects of local climate variability on transmission dynamics of cholera in Matlab, Bangladesh. *Trans R Soc Trop Med Hyg* 2009.
5. Koelle K, Rodo X, Pascual M, Yunus M, Mostafa G. Refractory periods and climate forcing in cholera dynamics. *Nature* 2005;**436**:696-700.
6. Pascual M, Rodo X, Ellner SP, Colwell R, Bouma MJ. Cholera dynamics and El Nino-Southern Oscillation. *Science* 2000;**289**:1766-1769.
7. Ruiz-Moreno D, Pascual M, Bouma M, Dobson A, Cash B. Cholera seasonality in Madras (1901-1940): Dual role for rainfall in endemic and epidemic regions.

EcoHealth 2007;**4**:52-62.

8. Huq A, Sack RB, Nizam A, et al. Critical factors influencing the occurrence of Vibrio cholerae in the environment of Bangladesh. *Appl Environ Microbiol* 2005;**71**:4645-4654.

9. Lipp EK, Huq A, Colwell RR. Effects of global climate on infectious disease: the cholera model. *Clin Microbiol Rev* 2002;**15**:757-770.

10. Pascual M, Bouma MJ, Dobson AP. Cholera and climate: revisiting the quantitative evidence. *Microbes Infect* 2002;**4**:237-245.

11. Faruque SM, Naser IB, Islam MJ, et al. Seasonal epidemics of cholera inversely correlate with the prevalence of environmental cholera phages. *Proc Natl Acad Sci U S A* 2005;**102**:1702-1707.

12. Lobitz B, Beck L, Huq A, et al. Climate and infectious disease: use of remote sensing for detection of Vibrio cholerae by indirect measurement. *Proc Natl Acad Sci U S A* 2000;**97**:1438-1443.

13. McCullagh P, Nelder J. Generalized linear models. London: Chapman and Hall, 1989.

14. Armstrong B. Models for the relationship between ambient temperature and daily mortality. *Epidemiology* 2006;**17**:624-631.

15. Bruzzi P, Green SB, Byar DP, Brinton LA, Schairer C. Estimating the population attributable risk for multiple risk factors using case-control data. *Am J Epidemiol* 1985;**122**:904-914.

16. Glass RI, Becker S, Huq MI, et al. Endemic cholera in rural Bangladesh, 1966-1980. *Am J Epidemiol* 1982;**116**:959-970.

17. Zuckerman JN, Rombo L, Fisch A. The true burden and risk of cholera: implications for prevention and control. *Lancet Infect Dis* 2007;**7**:521-530.

18. Stine OC, Alam M, Tang L, et al. Seasonal cholera from multiple small outbreaks, rural Bangladesh. *Emerg Infect Dis* 2008;**14**:831-833.

19. Cockburn TA, Cassanos JG. Epidemiology of endemic cholera. *Public Health Rep* 1960;**75**:791-803.

20. Hashizume M, Wagatsuma Y, Faruque AS, et al. Factors determining vulnerability to diarrhoea during and after severe floods in Bangladesh. *J Water Health* 2008;**6**:323-332.

21. Colwell RR, Brayton P, Herrington D, et al. Viable but non culturable Vibrio cholerae 01 revert to a cultivable state in the human intestine. *World Journal of Microbiology & Biotechnology* 1996;**12**:28-31.

22. King AA, Ionides EL, Pascual M, Bouma MJ. Inapparent infections and cholera

dynamics. *Nature* 2008;**454**:877-880.

23. World Health Organization. Using climate to predict infectious disease epidemics. In: Kuhn K, Campbell-Lendrum D, A. H, Cox J, eds. Geneva: WHO, 2005.

24. Altizer S, Dobson A, Hosseini P, et al. Seasonality and the dynamics of infectious diseases. *Ecol Lett* 2006;**9**:467-484.

25. Fisman DN. Seasonality of infectious diseases. *Annu Rev Public Health* 2007;**28**:127-143.

26. Grassly NC, Fraser C. Seasonal infectious disease epidemiology. *Proc Biol Sci* 2006;**273**:2541-2550.

27. Watson R, Zinyowera M, Moss R. The Regional Impacts of Climate Change: An Assessment of Vulnerability. Special Report of IPCC Working group II. Cambridge: Cambridge University Press, 1997.

FIGURE LEGENDS

FIGURE 1. Seasonal variations in the number of cholera cases per week and meteorologic and river level data in Dhaka, 1983−2008. The number of patients was halved between 1983 and 1995 because the proportion of patients enrolled in the surveillance system was 4% up to 1995 and 2% since 1996.

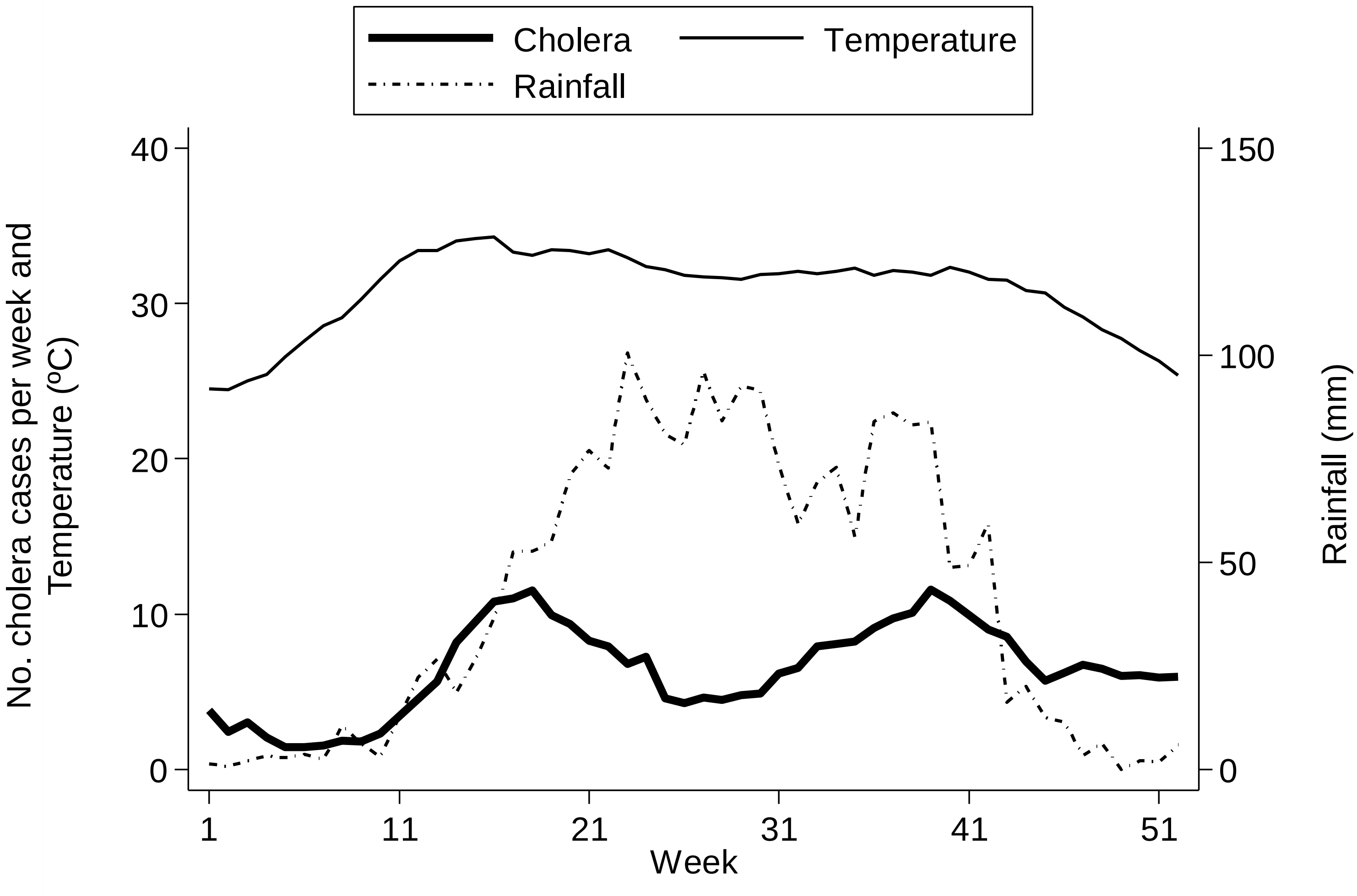
FIGURE 2. (A) Average annual pattern of relative risks predicted by each weather factor and their combination, and (B) the observed average seasonal pattern.

Table. Fractions of the number of cholera patients attributed to temperature, high rainfall and low rainfall allowing for season

	Attributable fraction		
	Total	Spring	Monsoon
Variable	% (95% CI)	% (95% CI)	% (95% CI)
Temperature	57.3 (52.4–60.8)	55.2 (48.1–60.0)	59.0 (55.9–61.4)
High rainfall	17.2 (13.0–21.0)	7.6 (5.6–9.5)	25.1 (19.0–30.4)
Low rainfall	8.3 (5.3–10.8)	18.4 (11.7–23.9)	0.1 (0.0–0.1)

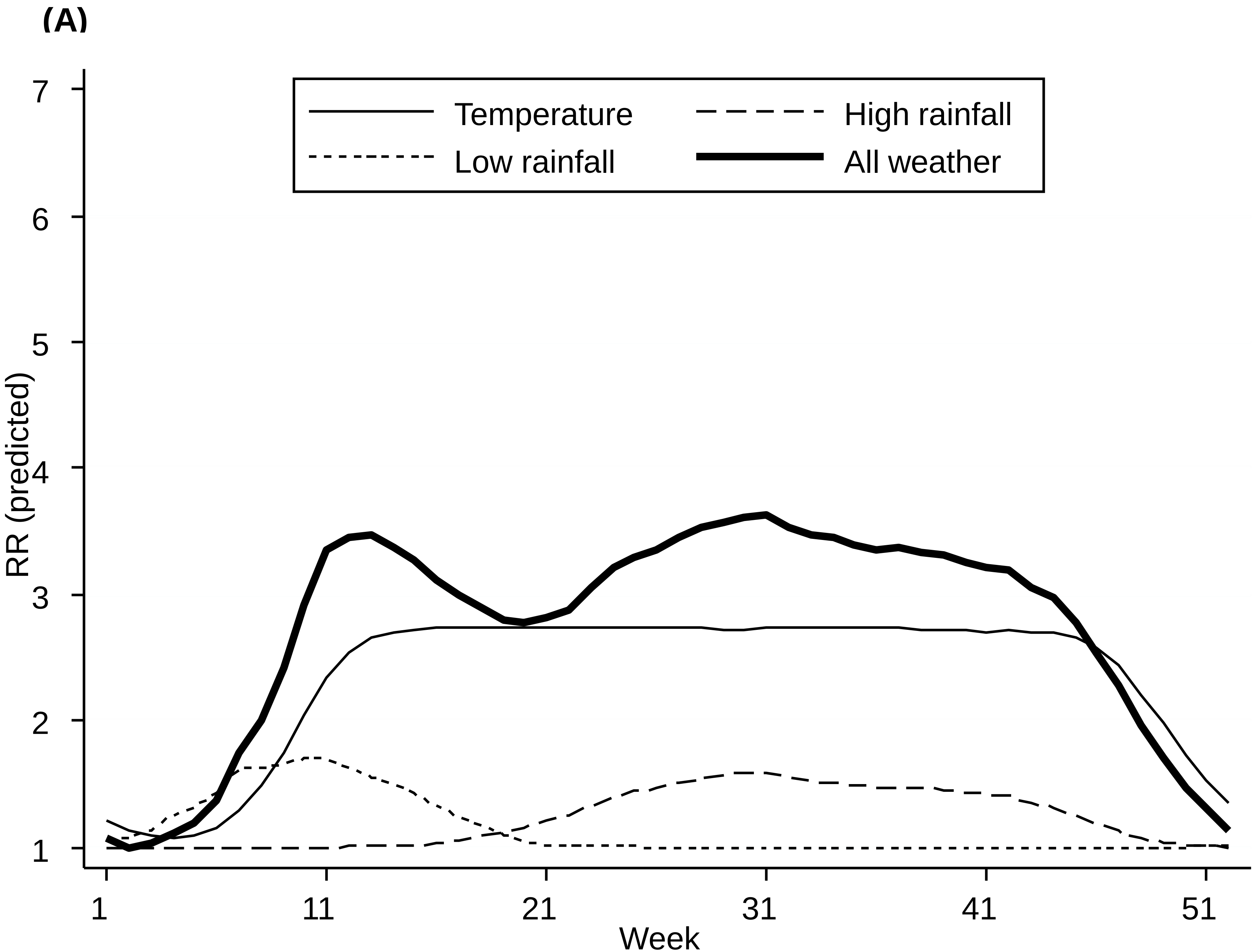
Spring indicates week 1–26; Monsoon, week 27–52.

Figure 1



Cholera
Temperature
Rainfall
No. cholera cases per week and Temperature (ºC)
0
10
20
30
40
Rainfall (mm)
0
50
100
150
1
11
21
31
41
51
Week

Figure 2A &2B



(A)
Temperature
High rainfall
Low rainfall
All weather
RR (predicted)
7
6
5
4
3
2
1
1
11
21
31
41
51
Week

(B)