Evaluating prospectively the impact of climate change on the occurrence of diarrhoeal diseases with emphasis on cholera: A generic research protocol

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Acknowledgement

This is a generic research protocol on prospective studies to assess the negative health impact of climate change on diarrhoeal diseases with emphasis on cholera and the capacity of health systems to cope with the consequences. The protocol has been prepared for WHO/SEARO by the National Institute of Cholera and Enteric Diseases (NICED), Kolkata. The protocol has been jointly prepared by Dr G.B. Nair, Director and Microbiologist, Dr A. Palit, Microbiologist, Dr A.K. Deb, Epidemiologist and Dr. S. Kanungo, Epidemiologist.

List of abbreviations

ADD	acute diarrhoeal diseases
ARI	acute respiratory infections
ARIMA	autoregressive integrated moving average
DALY	disability adjusted life years
ENSO	El Nino southern oscillation
GIS	geographic information system
GLS	generalized least squares
HA	health assistant
HW	health worker
IPCC	Intergovernmental Panel on Climate Change
IV	intravenous
LPS	lipopolysaccharide
NGO	nongovernmental organization
NICED	National Institute of Cholera and Enteric Diseases
OLS	ordinary least squares
PHC	primary health centre
SC	sub-centre
SEA	South-East Asia
SI	systeme internationale
SOP	standard operating procedure
SSH	sea surface height
SST	sea surface temperature
WHO	World Health Organization
WMO	World Meteorological Organization

1. Introduction

Infectious diseases, once expected to be eliminated as significant public health problems, continue to be the leading cause of death globally. Many factors have contributed to the persistence and increase in the occurrence of infectious diseases, such as environmental changes, societal changes, deteriorating health care, mass food production, human behaviour, public health infrastructure and microbial adaptation. Many diseases related to environmental factors have recently emerged worldwide and are of serious concern.

Climate change, if it occurs at the level projected by current global models, may have important and far-reaching effects on infectious diseases, especially those transmitted by poikilothermic arthropods such as mosquitoes and ticks. Although most scientists agree that global climate change will influence infectious disease transmission dynamics, the extent of the influence is uncertain. Some studies support that climate change has already influenced transmission of infectious diseases due to warming at higher elevations, including the retreat of tropical summit glaciers, upward plant displacement, elevational shifts in insect populations and vector-borne diseases, and upward shift of the freezing isotherm since 1970. Other studies, however, point out that in centuries past, vector-borne diseases as well as other infectious diseases occurred regularly in temperate regions in epidemic form during the summer months. Infectious agents like protozoa, bacteria, viruses and their associated vectors like mosquitoes, ticks and sand flies have a strong correlation with temperature fluctuation in terms of their reproduction and survival rates. Malaria and dengue fever with the more serious form of dengue haemorrhagic fever have a strong association with climate variability which is evident from past observations though for a short term (1-3). Some other vector-borne diseases which are affected by climate variability are Ross river virus in Australia, and plague.

According to the Global Burden of Disease (2002), the proportional mortality among children <5 years of age globally shows that Acute Respiratory Infections (ARI) and Acute Diarrhoeal Diseases (ADD) account for 18% and 15% respectively, of all deaths (4). In 55% of these deaths, the common factor is associated malnutrition (5).

Acute diarrhoeal disease is one of the most important health-related impacts linked to short- term and long-term changes in the climate. The frequency and intensity of extreme climate events such as droughts, floods and cyclones have a direct impact on the prevalence of diarrhoeal diseases. Studies from developing countries show that there are strong seasonal variations of diarrhoeal diseases in case of hydrological extremes such as water shortages and flooding. Water shortages cause diarrhoea due to perpetuation of unhygienic and poor sanitary conditions and flooding contaminates drinking water supplies.

Morbidity due to diarrhoeal diseases is also very high. Globally, 1.3 billion episodes of diarrhoea occur annually, mostly in children, with an average of 2-3 episodes per child per year (6). The global diarrhoeal disease burden was estimated at 6,24,51,000 DALYs (Disability Adjusted Life Years) lost in 2001 (7). The majority of the DALYs are from developing countries where children suffer from as many as 12 episodes of diarrhoea each year. In fact in certain areas with poor environmental sanitation, children are ill with diarrhoea for 10% – 20% of their first three years of life. In developing countries, up to a third of paediatric admissions in hospitals are due to acute diarrhoea.

Background

Climate change can no longer be considered simply an environmental or developmental issue. A greater appreciation of the human health dimensions of climate change is necessary for both the development of effective policy and the mobilization of public engagement. It has been hypothesized that environmental factors can directly or indirectly affect, survival, persistence and ability to produce such disease.

Many statistical models were deployed earlier to show the inherent association between change in the climate for a considerable period of time and prevalence of diarrhoeal diseases with special reference to cholera which is a sensitive marker for climate variation and some attempts were made earlier to show that environmental and climatic factors which cause seasonal patterns of infection are the key factors for the temporal variation of the disease, but that too in localized areas (8-10). In context to this theory, several researchers have established a link between heavy rainfall and flooding—whether resulting from El Niño-associated events or from other meteorological impacts—and subsequent outbreaks of infectious diseases (11). These climatic conditions are intermingled with other environmental and climatic conditions which also play a profound role in variation in the incidence of diarrhoeal disease.

Extreme meteorological events can easily disrupt water purification, storm water and sewage systems, as well as contaminate uncovered wells and surface water, leading to an increased risk of illness. These risks are even higher when a population lives in a low-lying area, where the land's hydrology causes draining tributaries to meet. Conversely, heavy rains and coastal events can also flush microorganisms into watersheds, affecting those up-coast as well. Sustainable development, that prevents deforestation and soil erosion, but influences water contamination by destroying the land's natural ability to absorb runoff, results in water-contaminating mudslides.

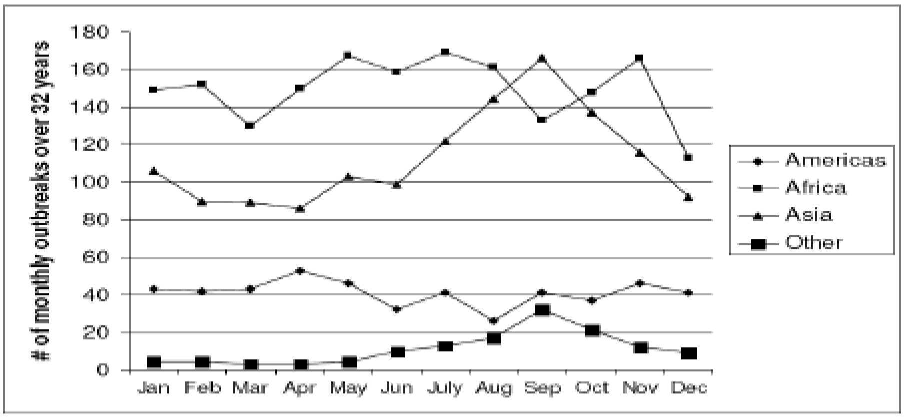
Global scenario

Considering the global scenario, climate variability and non-cholera diarrhoea also has a longitudinal relationship. Studies from Bangladesh show that the number of non-cholera diarrhoea cases increase with heavy rainfall, higher temperature particularly in lower socio-economic settings and poor sanitation (12). The influence of climate variation on diarrhoeal diseases is evident in the Pacific Islands also. Evidence shows that higher the temperature and lower potential water availability, higher is the diarrhoea and rural water sources get contaminated both in drought (stagnation) and flooding (13). The effect of El Nino in Latin America is seen in more hospital admissions which are directly related to excess increase in ambient temperature. In Peru, studies show that a 5^0C rise in temperature caused a 200% increase in diarrhoea-related admissions in 1997-1998 and a 1^0C rise in temperature caused an 8% increase in the risk of getting severe diarrhoea in children (14). In China, there is evidence of a 1^0C rise in maximum temperature causing an 11% rise in bacillary dysentery and a 1^0C rise in minimum temperature causing a 12% rise in bacillary dysentery (15). Even in England reports suggest that 1^0C increase in temperature causes a 5% increase in reported campylobacteriosis (16).

Relation between climate extremes and cholera outbreak pattern

Toxigenic *Vibrio cholerae*, the pathogen that causes cholera, is autochthonous to aquatic environs and is intricately associated with the microflora and fauna of aquatic environs. Cholera has the ability to spread as a worldwide pandemic and currently the seventh pandemic of cholera which started in 1961 is ongoing. Cholera infections vary greatly in frequency, severity, and duration, and its occurrence in different parts of the world is dynamic. In some South Asian countries it is endemic, in some parts like Africa and South America sporadic outbreaks occur, which is also a common feature in the endemic areas. Past studies have shown how cholera varies with seasons (17).

Monthly outbreak of Cholera by regions (18)



This temporal variation is believed to be due to the environmental and climatic factors. In the bimodal seasonal cycle of cholera cases and also in case of transmission of cholera there is a marked decrease during the early summer and monsoons, probably resulting from a reduction in cholera's environmental concentration along with a decrease in salinity affecting its survival (11). Cholera cases increase again and peak with a lag period after this season, as floods presumably concentrate the population on the decreased land area available and breakdown of sanitary conditions, promoting secondary transmission through the more direct faeco-oral route. The outbreak pattern of cholera varies with the seasons, mainly with heavy rainfall leading to water-logging and lack of potable water; the socio-economic, environmental and climatic factors are all intermingled. Besides rainfall, two remote drivers of inter-annual climate variability, the El Niño–

Southern Oscillation (ENSO),sea surface temperatures (SSTs) and chlorophyll a in the Bay of Bengal, are believed to influence cholera in Bangladesh (11). There is evidence of an increased role of inter-annual climate variability on the temporal dynamics of cholera based on the time-series analyses of the relationship between ENSO and cholera prevalence. A change in remote ENSO modulation alone can only partially serve to substantiate the differences observed in cholera. For the recent cholera series and during specific time intervals corresponding to local maxima in ENSO, this climate phenomenon accounts for over 70% of disease variance (19).

Evidence shows that there are some refractory periods during which climate-driven increases in transmission do not result in large outbreaks. Once the interplay of climate and disease dynamics is taken into account, there is clear evidence of the role of climate variability in the transmission of cholera. Meta analysis of 32 years of cholera data from WHO was attempted to see the association between cholera cases and different environmental factors like rainfall, sea surface temperature, humidity and altitude (20) which show a great variability in cholera incidence. This is associated with upper troposphere humidity, cloud cover and the level of solar radiation absorbed at the top of the atmosphere. In a retrospective case review of cholera-like diarrhoea during 1990-1991, it was hypothesized that El Niño-influenced ocean warming and the associated hyper growth of plankton contributed to the dispersal of *Vibrio cholerae* organisms—responsible for cholera—along the Pacific coast of Peru (14).

Additional factors like ENSO, North Atlantic oscillation, sunlight, temperature, pollution, level of rainfall, and some socio-economic and demographic factors are responsible for outbreaks (21). An inverse correlation between environmental phage concentration (post-flood and post- monsoon periods) and epidemics has been also postulated recently (22).

Several tools and models were used in the past like satellite imaging to show the association of cholera with sea surface height and sea surface temperature (23). Host pathogen dynamics suggested in 2005 measure the association between seasonal drivers and rate of transmission of the disease (24).

Despite a strong suspicion and positive suggestion by some studies, many of these earlier studies did not find any definitive association between climate change and the occurrence of diarrhoea and failed to explain the non-existence (or even existence) of such an association. Presumably, this occurred due to the non-availability of data on other non-climatic factors (such as human behaviour and socio-economic factors) that may also positively or negatively contribute to the occurrence of diarrhoeal diseases. The important non-climatic factors with which diarrhoea is associated include : safe water supply, adequacy of available water (per capita water), adequacy of sanitation, nutritional status, level of urbanization, poverty, childhood feeding practices (including breastfeeding), immunization (especially against measles) and vitamin A supplementation (25-30). However, the first six factors mentioned above can act as potential confounders in the current context, since the others are presumably not associated with climatic factors. Hence, along with data on diarrhoea and relevant climatic factors, simultaneous collection of such non-climatic data is strongly recommended to allow for adjustments of the estimated effects of climate changes on diarrhoeal diseases.

2. Objectives of this protocol

(1) To describe the time-series characteristics of long-term data on diarrhoea and appropriate climatic and non-climatic factors.

(2) To identify and test a range of climatic and non-climatic indicators as potential co-variables in predictive models of diarrhoeal diseases, including occurrence of diarrhoea outbreaks.

(3) To assess preparedness of a country or region in dealing with possible negative impacts of climate change on diarrhoeal diseases.

Since the association between climate change and the incidence of cholera has been suggested by many studies, these objectives will also be applied separately for cholera-specific diarrhoea.

To meet these objectives, one can utilize existing data, collect data prospectively, or use a combination of both retrospective and prospective data. The key points are that these data need to be of adequate quality and quantity, and collected in a way that makes comparisons across time and region valid.

For prospective data collection, a surveillance system for diarrhoeal diseases is preferable, which can also be utilized for other public health purposes such as to determine distribution of diarrhoeagenic pathogens and their drug resistance patterns, emergence of new pathogens etc., if adequate facilities are available. The preparedness can be assessed by checking the existence of necessary infrastructure and logistics relevant for the purpose, which is presented in this protocol in a tabular format.

The methodologies followed in this protocol assume setting up a diarrhoeal diseases surveillance system (or using an existing system, if reliable and timely data can be generated through that system) along with prospective collection of climatic and non-climatic data through existing or newly built systems.

It should be noted that all data (on diarrhoea, climatic factors and non-climatic factors) should be collected in a way that allows estimation of association among these variables – for example, the frequency of collection should be such that weekly/monthly (or other suitable time interval) data are available for at least diarrhoea occurrences and climate variables (collection of non-climatic factors e.g. socio-economic factors may have different, usually longer, periodicities). Similarly, to compare data over time, application of the same methodologies and instruments (including various forms and logs) is imperative for the whole duration, as is the need to have regular quality control systems in place.

Thus, this protocol focuses on three major activities that will operate simultaneously to gather necessary information for establishing climate-diarrhoea relationship:

(a) Collection of diarrhoea-related information through a surveillance system

(b) Collection of necessary climatic data, and

(c) Collection of selective non-climatic data from the same population under surveillance.

In addition, some information about diarrhoea outbreaks can also be collected to test the outbreak prediction models.

The three major activities as mentioned above are discussed in detail in the following sections.

3. Surveillance of diarrhoeal diseases

Disease surveillance provides a means of monitoring disease incidence over time and, depending on the nature of the system, may be an appropriate instrument for detecting unusual incidence patterns. Thus, surveillance may allow early detection of an epidemic rather than predicting the onset of an epidemic. However, when used in conjunction with climate data, it may be possible to forecast the occurrence of an outbreak in a specified area as well. Since lack of adequate and acceptable disease data is a more common limiting factor than lack of climate data, maintaining and strengthening disease surveillance systems for monitoring the incidence of diarrhoeal diseases is a prerequisite in the present context. High-quality data on the incidence of diarrhoea, covering long periods, are essential for generating and refining models relating impact of climate chane on diarrhoeal diseases.

An important first step will be to assess current approaches to diarrhoea surveillance and the quality, quantity and completeness of associated disease data. In many cases, existing disease data may be suitable for model development and the system itself quite appropriate for early detection of an epidemic. In other situations, existing systems may need extensive modification, either in the way in which disease data are collected (e.g. case detection and diagnostics), or in the manner in which data from individual health facilities are collected, aggregated and communicated to higher levels in the health system.

3.1 Deciding on types of surveillance

There are several considerations before setting up a new surveillance system or using an existing one. Decisions need to be made about hospital-based or community-based systems, and active or passive systems. One needs to understand that different types of surveillance will generate different levels of precision in the data, and at different costs. For hospital-based data collection, one may consider whether hospital-based data would provide an accurate representation of morbidity related to the disease. If not, data collection should be extended to include information from other clinics or even mobile care sites. For diseases like diarrhoea, it should be kept in mind that many of the milder cases may not attend hospitals or clinics – thus a proportion of cases may remain unknown. Community-based surveillance, on the other hand, although providing more complete information, would be more (sometimes prohibitively) expensive. In situations where resources may be finite, monitoring only at sentinel sites may be more appropriate than using a comprehensive "all-sites" approach. The critical issue is whether selected sites will provide a reasonable representation of the health outcomes being monitored. In places where laws or regulations regarding mandatory reporting of diarrhoea cases could be enforced (including in the private sector), obtaining periodic reports about disease occurrence from the care providers could be a comparatively inexpensive option. However, for various reasons this is extremely difficult to implement in countries where the burden is in fact more. Finally, for active vs. passive systems, one may prefer active solicitation of information that may provide timely and appropriate information on the disease, including ability to capture milder and shorter-duration cases, in contrast to a passive surveillance system that collects data only on a routine basis. Moreover, in communities where there are several health care options (such as a number of private health practitioners and clinics), case capture through a passive system may be inadequate and biased. However, active surveillance would obviously require more resources. Thus, understandably, it would be very difficult to formulate an "ideal" surveillance system that could be equally applicable to many different countries or regions. Nevertheless, a common approach is discussed in the current protocol that will presumably not be very difficult to implement, will provide sufficient data for our purposes and will allow data to be compared across countries or regions.

In this protocol, we assume using existing primary health care infrastructure and personnel, e.g. health care personnel in primary health centres (PHCs) and sub-centres, for the proposed surveillance and discuss in detail a procedure for community-based facilitated passive surveillance system for collection of diarrhoeal data.

3.2 Case definitions

Another important issue that needs careful attention is to use uniform criteria to define at least two things - "cases" of diarrhoea and "episodes" of diarrhoea. The definitions should be appropriate and acceptable to the scientific community and also easy to use in a community setting. Without such definitions being uniformly implemented, the resulting data would be impossible to compare across sites and/or over time. The definitions that are suggested for the purpose of this protocol are as follows –

"Cases" of diarrhoea

Diarrhoea is the passage of three or more loose or liquid stools per day, or more frequently than is normal for an individual. For smaller children, mothers' perception about increased stool frequency and a change in consistency will be used to determine cases of diarrhoea.

"Episodes" of diarrhoea

Distinct diarrhoea episodes will be considered for each subject when occurring after a symptom-free period of at least one week.

"Cases" of cholera

A case of cholera will be defined as having acute non-bloody diarrhoea with a positive dipstick test for cholera, where –

> *acute bloody diarrhoea* will be defined as "diarrhoea with visible blood of acute onset".

3.3 Choice of site and population for surveillance

While selecting suitable site(s) and population to assess effects of climate change on diarrhoea, we need to consider three things:

(a) Appropriate site(s) and one or more population groups suitable for the purpose (as described in the box), according to country-specific situations.

(b) Availability of climatic data for such site; if resources are not a constraint, constructing a climate station to obtain necessary climatic data around the area would be an option (if such a facility is not already available). Otherwise, the best available site (according to the above description) around an existing climate station can be chosen.

(c) The population should be stable as far as possible with little inward/outward migration; of course, if such migration does not change the population structure and characteristics too much, it is also acceptable for such surveillance.

……..It is the high consumption lifestyles of wealthy people that drive climate change. But it is the low-income groups in low-income nations, with almost negligible contributions to climate change, which are most at risk from its impact.

……..The populations considered to be at greatest risk are those living in small islands, mountainous regions, water-stressed areas, mega-cities and coastal areas, particularly large urban and peri-urban agglomerations in delta regions in the SEA Region, as well as poor people and those unprotected by health services.

[*Source*: Protecting Health from Climate Change / World Health Day, April 7, 2008]

3.4 Appropriate size of the population

The population size under surveillance should be adequate to generate a sufficient number of cases of diarrhoea so that the climate-diarrhoea association can be established. If, in addition, cholera is also a subject of interest, a larger population would be required to generate a sufficient number of cholera cases. The chosen population size, birth and death rates in the specific area, net migration rate, case capture rate and expected incidence of diarrhoea would indicate the expected number of diarrhoea cases from that population. To obtain the expected number of cholera cases, one would additionally need information about the proportion of diarrhoea that is diagnosed as cholera in that area and the proportion of detectable cases from whom a stool specimen could be collected. For the purpose of this study, a primary health centre (PHC) coverage area (with approximately 30 000 population) is suggested as the unit of study.

3.5 Collection of diarrhoeal data

Types of diarrhoea data to be collected

The collection of data would be such that a minimum set of variables has to be covered to allow establishing a climate-diarrhoea connection. At the same time, these should be easily measurable by health workers. Additional data can also be collected from the system depending on other local needs and interests. This protocol suggests collection of at least the following data (apart from subject identification data) for the subjects under surveillance if they develop diarrhea:

Date / time episode started	Date / time episode ended
Type of diarrhoea / stool character	Cholera test result (if tested)
Frequency of stool (in the last 24 hours)	Outcome (cured/died/others)
Severity (assessed only by IV fluid requirement)	

If facilities are available, a stool specimen can be obtained from these cases and tested for cholera as outlined under the laboratory procedures.

Usually, monthly time-series of incidence of diarrhoea (or cholera) comprises disease data for the analysis. However, other parameters such as duration of diarrhoea or severity can also be assessed to determine any changes in relation to climate variations.

Frequency of data collection

To assess changes in disease incidence with changes in climate, it is imperative to collect data at similar intervals. For example, if one collects weekly climatic data, then data on disease occurrence should also be collected weekly. However, it should be noted that collecting data very frequently may not be meaningful as far as disease occurrence is concerned. For example, if data are collected daily or weekly, there may not be enough cases of diarrhoea – in fact, there may be no case at all in many of the days or weeks (unless a huge population is selected). Thus, it will be useful to collect only monthly data, which is sufficient to serve the purpose.

In any case, it will be wise to fix a schedule for health workers for collection of information at the very beginning. This is to ensure that the surveillance (and hence data collection) follows a specific intensity throughout. Otherwise, due to variations in the intensity of the surveillance process itself, there will be variations in the number of detected cases – further obscuring the true nature of climate-diarrhoea relation. A sample guideline has been provided in the box in the next section, which can be modified according to locally prevailing situations.

Methods of data collection

Community-based surveillance will be conducted by health workers (HWs), at the primary level of health care delivery. They will be trained adequately for this purpose. They will collect family-level baseline information about the population under their coverage area (usually a sub-centre area) at the beginning and will update them every year. This baseline information will include relevant demographic and socio-economic characteristics, child immunization practices, sources of drinking water, and sanitation facilities. Unique IDs will be provided to the subjects to keep track of future diarrhoea episodes and outcomes, including laboratory results. After the initial baseline data collection, HWs will visit the families monthly to record occurrences of diarrhoea during the past month on a structured information sheet and motivate members to attend the sub-centre or the PHC if anyone suffers from diarrhoea. In case they encounter anyone with diarrhoea during the visit, they will try to get a stool specimen either themselves or by taking the subject to the nearest health facility and also collect relevant information about the episode. Specimen may also be collected in the sub-centres and in the primary health centres (PHCs) during working hours. Thus, this process will enable simultaneous collection of data on non-climatic risk / preventive factors for diarrhoea as well. The activities of the HWs will be supervised by their supervisors (usually health assistants at the PHCs), who will check the correctness, completeness and legibility of collected data (in constrained situations, a fraction of HW-collected data can be checked). In addition, 5%-10% of the randomly selected subjects / families may be re-visited by the supervisors for data verification. The laboratory technician at the PHC will note the characteristics of the stool specimen and test it to detect cholera cases according to the procedures illustrated under the laboratory methods. Collection of data and stool specimen will be preceded by appropriate informed consent procedure at the community or individual level as per the prevailing ethical guidelines of the respective countries.

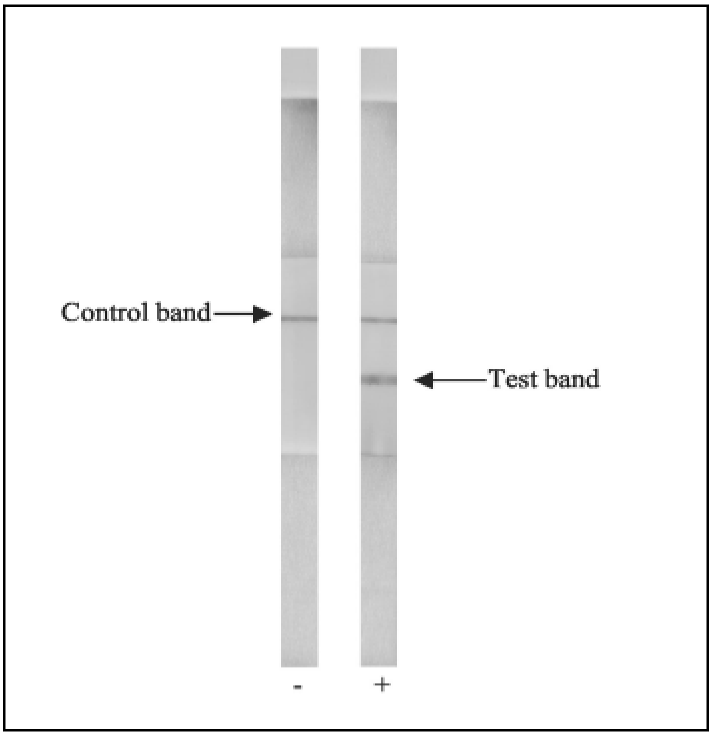
> Usually, one sub-centre covers a population of 5000 (3000 in backward and hilly areas) and two HWs (one male and one female) are posted in the sub-centre (sometimes accompanied by another voluntary part-time worker). Thus, each health worker will be responsible for looking after around 1500-2500 individuals (or 300-500 families). Thus, assuming 20 working days in a month, they need to visit 15-25 families per day.

3.6 Duration of surveillance

Although ideally, as per standard definition of 'climate', the duration of the surveillance should be at least 30 years, shorter duration studies (such as 5-10 years) are also acceptable. While conducting the surveillance prospectively, one can also use retrospective data for a certain time period (say the last five or 10 years' data) if necessary data are available for that period and at the same time it is reasonable to assume that those data were collected using similar methods and techniques as in the prospective study.

3.7 Laboratory procedures

Stool samples will be collected either at the home by trained health workers or at the nearest health facility. Information on the macroscopic appearance of stools will be recorded at the health facility. In addition, at all health facilities, the newly designed commercially available cholera dipsticks will be used. The dipstick test utilizes monoclonal antibodies specific to *V. cholerae* O1 and O139 lipopolysaccharide (LPS) and colloidal gold particles based on a one-step, vertical flow immunochromatography principle. The detection threshold with purified LPS is 10 ng/ml for *V. cholerae* O1 (31). The dipstick test is performed by pipetting 200 µl of bulk stool into a fresh tube into which the test strip is inserted. The test strips will be read after 10 minutes of immersion in the stool. The tests will be defined as "positive" when both a test line and control line appear on the test strip (32). Health workers or laboratory workers will be trained for a defined period before the study starts to perform and read the results of the dipstick by a consultant from the National Institute of Cholera and Enteric Diseases, Kolkata with prior experience in the use of the assay.



Two dipsticks showing typical negative and positive results after being kept for 10 min. in secretory diarrhoea stool samples. (*J Clin Microbiol* 2003, 41: 3939 - 3941).

4. Collection of climatic data

Climate summarizes the average, range and variability of weather elements e.g. rain, wind, temperature, fog, thunder, and sunshine observed over many years at a location or across an area. Thus, in order to understand the climate better, one may need to collect a wide range of data from the atmosphere, oceans and land surface.

4.1 Types of climate

The word "climate" has different meanings depending on the size of the domain, such as the climate of a forest, the climate of a city, or changes in the global climate. It is helpful to distinguish the 'microclimate' of a *site* (e.g. a climate station) from the 'topoclimate' of a *locality* (like a valley or a city), the 'mesoclimate' of a *region*, the 'synoptic' climate of a *continent*, and the 'global' climate of the whole planet. The importance comes from the fact that if we want to associate diarrhoeal data from a locality with, say, climate data for the whole country, we may not be able to find any association even if there truly exists such an association (or vice versa). Thus, again it is emphasized that both climatic and disease data should come from the same locality or domain as far as possible.

4.2 Measuring climate data

Understanding the "climate" requires reliable, long records of daily values obtained with standard equipment. The instruments must be properly installed in suitable places, carefully maintained and conscientiously observed. Even then it is necessary to consider likely errors in the measurements.

The operation of a 'climate station' requires a set of instruments, installed to measure a particular "microclimate" – usually selected as representative of the surrounding "topoclimate" or "mesoclimate". A climate station provides less information than a weather station – only daily figures on dry-bulb and wet-bulb temperatures, maximum and minimum temperatures, rainfall, amount of cloud, snow depth, current weather type and visibility. Optional measurements include the number of hours of sunshine daily, the grass minimum temperature, the wind direction and speed, and atmospheric pressure. 'Ancillary' or 'cooperative' stations involve a yet smaller range of measurements, primarily for agriculture. They include thermometers to measure soil temperature, maximum and minimum thermometers for screen temperatures, a sunshine-duration recorder, a humidity meter, a rain gauge and an evaporation pan. Other equipment desirable at an agro-climate station include a dew-meter, a recorder of wind speed and direction, a rainfall recorder and an instrument to measure solar irradiance.

To serve the purpose of this protocol, the participating climate station(s) should be able to measure at least three indicators – minimum and maximum temperatures, rainfall and humidity. The daily measurements on these variables will be transformed into, for example, average monthly measurements before being used in the analysis.

Additionally, if remote sensing facilities are available (or such data are procured from appropriate sources), one can also use measurements on variables such as chlorophyll-a, sea surface temperature (SST), sea surface height and ENSO.

4.3 Units of measurement

It is unfortunate that most of the literature on climatology is based on superseded units. There is a muddle of Fahrenheit and Celsius, calories and joules and British Thermal Units, miles per hour and knots, and so on – quite apart from special units concocted for particular aspects of climatology such as the “clo”, “acre-foot", Met and Langley. However, to be able to compare data from different sites and / or different periods, it is desirable to maintain uniformity in use of units of such measurements. This protocol suggests the use of Systeme Internationale (SI), based on metre, kilogram and second. The convenience of this decimal system lies in the ease of calculations, of expressing and comparing values, and a general simplification of terms.

5. Collection of non-climate data

Even where linkages between diarrhoea and the climate are relatively strong, other non-climatic factors may also have a significant impact on the timing and severity of the disease and outbreaks. Distinguishing underlying trends of these factors from inter-annual variability should help to avoid disease variations being attributed incorrectly to climate. Testing for such non-climatic influences on disease fluctuations is dependent on the availability of appropriate data. More importantly, in practical terms, incorporating the data available for non-climatic variables should lead to greater accuracy in predictive models for diarrhoea-climate association, especially if one wants to develop an early warning system for outbreaks.

5.1 Types of non-climate data

Many non-climate factors can influence the occurrence of diarrhoeal diseases. The factors that can relatively easily be measured include changes in population size and age structure, population mobility (e.g. net migration rate), economic status, immunization practices, sources of drinking water (or proportion of population with access to safe drinking water), proportion of population with adequate sanitation facilities etc.

Apart from these, there are several other factors that will be a little difficult to measure, such as changes in public health services, land use and travel patterns.

5.2 Measuring non-climate data

Most of these non-climatic data can be obtained through interviewing the members of the household (either all members or a representative sample thereof). Thus, it is possible to incorporate this into the community-based surveillance system itself, where the same workers collect these data, but with a different (longer – half-yearly or yearly) periodicity (because these data, e.g. socio-economic factors, usually do not change frequently over time). One can also obtain these from government or other appropriate sources – for example, data on access to safe drinking water and adequate sanitation facility, immunization coverage for eligible children, persons living below the poverty line etc. can be collected from government records.

5.3 Frequency of measurement

It is not a good idea to collect non-climatic data (e.g. socio-economic data) with similar frequency as diarrhoea data, since these characteristics are not expected to change so frequently. Thus, it may be enough to collect these data on a yearly basis (possibly during yearly census of the population under study to note any changes in the population structure itself).

6. Collection of outbreak data

Current strategies for controlling outbreaks of diarrhoea largely depend on on-going surveillance to detect new outbreaks, followed by a rapid response to control that outbreak. However, climate forecasts along with environmental monitoring could potentially be used to identify areas at risk for diarrhoea outbreaks. This approach could potentially prevent occurrence of such outbreaks by timely initiation of appropriate efforts. Often our limited understanding of most climate-disease relationships incapacitates us to develop an early warning system. However, for cholera, and may be for diarrhoea as a whole, such a system will be feasible to develop, appreciating the fact that there will always be an element of unpredictability in climate variations and occurrence of outbreaks.

6.1 Sources of outbreak data

The purpose of collecting outbreak data is to validate predictive models developed to predict occurrence and/or extent of diarrhoeal outbreaks. The outbreak data on diarrhoea can be collected both from records or reports of past outbreaks and also prospectively through the surveillance system. However, it should be borne in mind that there may not be a sufficient number of outbreaks within the surveillance area to establish a strong climate-outbreak relationship. Hence, supplemental data from neighbouring (preferably similar) areas may have to be collected. Once a relationship is established, its predictability can be tested with future outbreaks in those areas.

6.2 Measuring outbreak data

Several aspects of diarrhoeal outbreaks can be studied, such as seasonality (month / season), duration of outbreak (from onset to extinction, in days), number of cases (with age distribution), proportion of severe cases (as judged by requirement of IV fluids), and fatality (case-fatality). At the same time, appropriate climatic and non-climatic data as mentioned earlier would be needed for the validation purpose.

7. Optional data collection

7.1 Optional data on diarrhoea

Apart from diarrhoea data mentioned earlier, one can collect additional data according to requirements. These include data on mortality from diarrhoea, patterns of pathogen isolation and drug sensitivity. If sufficient data are available, these can also be checked for association with the climate.

7.2 Optional data on climate

It is now well known that many ecological parameters such as sea surface temperature, phytoplankton densities etc. are intimately associated with diarrhoeal occurrences, specially cholera. Unfortunately, routine observations of these ecological data are rare. However, new remote sensing technologies are rapidly expanding the opportunities to monitor many of these parameters such as sea-surface temperature (SST), sea-surface height and chlorophyll concentration of water. The geographic information system (GIS) provides a framework that facilitates integration of these remotely sensed parameters with disease data and thereby create maps of risk of disease in different areas. The table below shows some environmental and climate factors associated with risk of exposure to *Vibrio cholerae* and how they can be measured.

Some environmental and climate factors associated with exposure to Vibrio cholerae

Factors to be studied	Possible approaches for measurement
Chlorophyll-a and/or turbidity associated with rainfall	Remote sensing
Influence of temperature and water salinity on the growth of Vibrio in the copepod	Bacterial growth curves
Concentration of bacteria in the copepod	Plankton sampling and immunofluorescence microscopy
Number of copepods transmitted upstream and in a glass of water	Straining and examination of the water supply
Influence of rainfall and run-off on salinity and nutrients leading to algal blooms	Population dynamic modeling
Influence of temperature on phytoplankton growth	Population dynamic modeling

8. Data analysis and archiving

8.1 Analytic strategies

There can be a number of approaches to determine the relationship between climate and diarrhoeal diseases (as well as cholera), such as (a) analysis of observational data (retrospective or prospective), (b) model-based predictions of future events and (c) other more rigorous approaches like risk assessment. The interpretation of results from these different approaches may not have similar strengths or predictive powers; while some are more relevant to generate new hypothesis, others are useful to test them. Here we discuss mainly the strategies for analysis of collected data – the actual analytic procedures will depend on the amount and characteristics (e.g. distribution) of available data.

Definition of predictors

Climate data: Usually obtained as daily values (e.g. daily maximum and minimum temperatures); monthly averages will be calculated from these daily values and used as climatic predictors.

Non-climate data: Yearly values for the population on –

Population size and age distribution (specially, under-5 population)

Proportion below poverty line

Proportion having access to safe drinking water

Proportion having appropriate sanitation facility

Proportion of eligible children having received measles immunization.

Definition of endpoints (outcomes)

Incidence of diarrhoea:

(Total no. of episodes detected in a month)/(Total population under study)

Age-specific incidence of diarrhoea, e.g. incidence among under-5 children:

(Total no. of episodes among under-5 children in a month) / (Total under-5 children under study).

Severity of diarrhoea: Proportion of severe cases –

(Total no. of episodes requiring IV fluid in a month)/(Total no. of episodes detected in that month).

Incidence of cholera: Will be measured for non-bloody diarrhoea only -

[(Total no. of cholera dipstick test positive)/(Total no. of stool specimen tested) *

(Total no. of non-bloody diarrhoea episodes)]/(Total population under study).

Case fatality from diarrhoea:

(Total no. of deaths due to diarrhoea) / (Total no. of episodes) * 100.

* [Total population and total under-5 children will be updated each year; incidence of cholera may be calculated separately for under-5 children; case fatality can be calculated for cholera separately and also within specific age group (e.g. under-5) for diarrhoea and cholera].

Data analysis

The predictors and endpoints, as defined above, will be analyzed next to describe their patterns individually. Since these data are collected repeatedly over a long time, they represent a set of time series data. The goals of time series analysis are *description, explanation, prediction* or *control*. The *descriptive* analysis is used to understand the underlying patterns of a given time series, whereas to *explain* the dependence of a response (outcome) time series Y_t on a number of predictor series X_{1t}, … ,X_{pt} we typically use regression analysis taking into account the lack of independence among the time series observations. To *predict* a future response using an observed series, we can regress the response at a given time on preceding responses and possibly also on covariates that are known to influence.

Descriptive analysis

Here, we would like to understand the main features of each of the respective time series (i.e., for each predictor and outcome). A time series (i.e., each data value in the series) may be composed of three main components (sometimes with an additional "cyclical" component) –

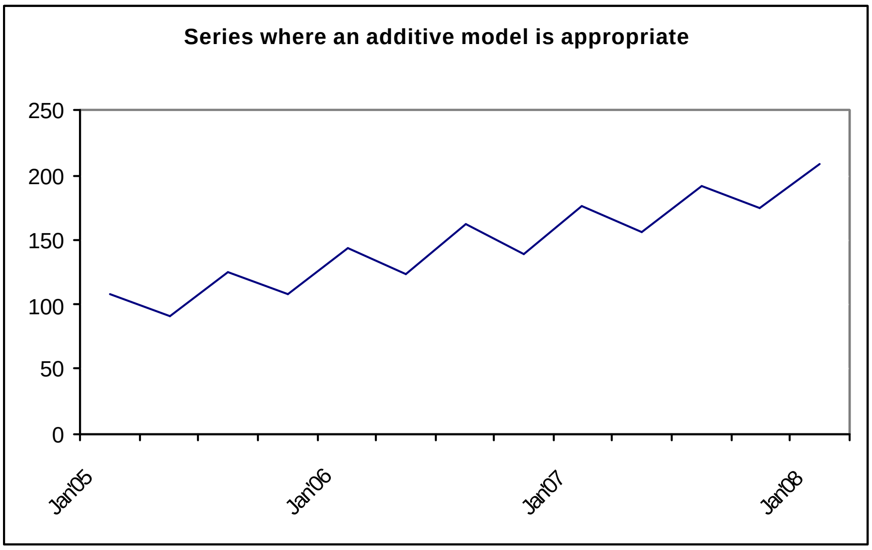
(a) The "trend" component

(b) The "seasonal" component, and

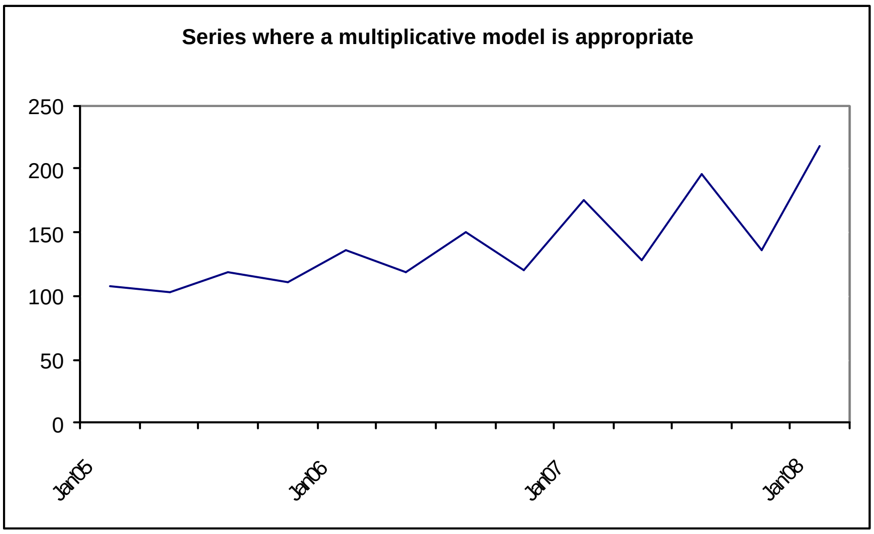
(c) The "irregular" component.

The "trend" describes a long-term movement in a time series; it denotes the underlying direction (upward or downward) and the magnitude of change in a time series, controlling for other components. In weekly or monthly data, the "seasonal" component (or seasonality) denotes the variations in time series depending on the time of the year. Seasonality describes any regular fluctuations within less than a year. The "irregular" component, on the other hand, denotes irregular (random) fluctuations in time series; it is the left-over when other components in the time series are accounted for.

Before proceeding further, it would be desirable to understand how the different components make up the data values in time series – are they *additive* (i.e., data value = trend + seasonal + irregular) or are they *multiplicative* (i.e., data value = trend × seasonal × irregular)? A simple look at the values graphically may help solve the problem, as shown in the following two figures.



When the "seasonal" component does not vary over time (note that although the trend is increasing, the magnitude of seasonal fluctuations within each year remain similar), an additive model will usually be the best.



On the other hand, when the magnitude of the “seasonal” component increases with increasing trend, a multiplicative model will usually be suitable.

The seasonal component can also be compared quantitatively. First, the trend component is obtained by some smoothing technique, usually using moving averages. Then the trend can be examined in two ways – (a) by looking at the moving average line at different points or (b) by fitting a regression line (linear, quadratic or other such as a non-linear regression line, as seems appropriate from the data). When the trend values (obtained through moving averages) are subtracted from respective data values, one gets the seasonal and irregular components together for each value. If we again compute moving averages for these values, we would get the seasonal component for the series. To control for irregular components (random fluctuations) in the data, one can employ exponential smoothing.

Thus, checking the time series plots with “trend” for the predictors and outcomes and comparing them would indicate the patterns of changes in each variable with time and show if any relation exists among them. Sometimes an appropriate time lag is also applied in the analysis.

Explanatory analysis

When the objective of analysis is *explanation* – i.e., how the explanatory variables (climatic and non-climatic) influence an outcome (diarrhoea or cholera) over time, we can model the dependence of the outcome Y_t on one or more predictor time series X_t. This is done using *regression analysis*. In a standard regression model the responses are assumed to be independent of one another, whereas with time series data, neighbouring values of Y tend to be correlated. This “autocorrelation” must be taken into account to make valid inferences. Specifically, in such situations we would like to use models based on generalized least squares (GLS) rather than using ordinary least squares (OLS) methods. Several approaches may be taken, based on the characteristics of obtained data – one common approach is using the ARIMA model that incorporates trends and temporal autocorrelation into a single model, especially when the time series data are non-stationary (i.e., display a clear trend).

Identification of climatic and non-climatic risk factors for the outcome or risk assessment also involves modeling. There are two major approaches to such modeling: statistical and biological. Statistical models are used to determine the direct statistical correlations between predictor variables (e.g. climate) and the outcome of interest (e.g. disease incidence). Biological models attempt to provide a mechanistic process in which the effects of climate on the population dynamics of pathogens and vectors are represented. Thus, biological models potentially offer greater insights into the mechanisms driving variations in disease incidence, but require a more extensive understanding of the effects of climate on all aspects of pathogen and vector dynamics.

As a result, such models have rarely been applied. Whichever modeling approach is used, it is important to take non-climatic factors into account. Failure to incorporate such influences can lead either to variation in disease incidence being incorrectly attributed to climate effects and/or to poor predictive accuracy.

Predictive analysis

The relationship between disease incidence and the climate factors identified above can be quantified in a statistical or biological model, which may subsequently form the basis for future predictions of disease occurrences or outbreaks. Before modeling can be initiated, however, it is necessary to ensure that both disease and explanatory data are available at appropriate spatial and temporal resolutions and for a sufficient time-frame.

Generally, when any disease exhibits large interannual variability, it can be considered as an epidemic. However, the transmission of many infectious diseases (including diarrhoea) also varies markedly by season. Thus, fluctuations in disease incidence are considered epidemics only if the number of cases exceeds a certain threshold. A variety of epidemic detection thresholds have been used in the past; probably the most commonly used definition of an outbreak is a situation where reported cases exceed a threshold of 1.96 multiplied by the standard deviation of the mean from a sufficiently long-term observation. In any case an epidemic is detected best by examining continuous long-term datasets; therefore setting up a surveillance system is an important preliminary requirement.

For predictions, the simpler empirical statistical models are based on relationships between climate and diarrhoea-related variables that have been estimated from observational studies. Such empirical data on patterns of variations are used to project how the studied variables may change in the future – specially, based on the threshold for outbreak and predictions from the model, we may want to know whether any outbreak is likely to occur within a specified time and place. This capability comes from the fact that now-a-days it is possible to predict climatic conditions well in advance – at least for the next seven days (for some countries / areas, even for the next month). Thus, putting these future climate values in the prediction model can determine the occurrence of an outbreak in that future time period. The sensitivity, specificity and predictive values for such models may be determined by cross-validation methods, including real observations in future (and also in the past, if sufficient data are available for validation). Often these models take the shape of a complex multivariate model that considers various environmental and other factors affecting the risk of diarrhoea. This modeling approach may be limited if insufficient data points are available to calibrate the projections, and hence, making the results difficult to validate. However, these are often simpler to use and less data demanding than the mechanistic (process-based) models where the forecasted changes in disease risk are based on interactions of physical and biological variables. Whatever models are used, it is desirable to keep it as simple as possible, while keeping necessary variables in the model. Availability of data at appropriate scales should be taken into account while building the model. Other important issues regarding the available data would be considerations for measurement errors and reporting bias.

To summarize, the analytical process involved in quantifying climate–disease links can be separated into five main steps:

(1) Fitting trend lines and sine–cosine waves (or similar) to remove long-term trends and potentially non-climatic seasonal variation from outcome and predictor variables.

(2) Testing, by parametric or non-parametric means, for correlations between climate variability and variability in the outcome variable.

(3) Using cross-validation techniques to test the robustness of the model.

(4) Using the derived equations to make predictions for subsequent time points not included in the original model.

(5) Measuring levels of agreement between predictors and outcomes.

8.2 Data safety and archiving

Since data will be collected for several years, proper safety and confidentiality issues must be addressed carefully. Maintenance of electronic databases, and if possible, an electronic reporting system is desirable with appropriate data back-ups. Back-up and hard copies of data should be archived so that they are safe from fire, pests and other damage but at the same time easily retrievable.

9. Quality monitoring

9.1 Surveillance data

To ensure quality of surveillance data, several steps may be taken. For example, all collected data may be checked by supervisors for legibility, correctness, consistency and completeness. In addition, 5%-10% randomly selected families may be revisited by supervisors and data may be collected in duplicate and compared with health worker collected data for accuracy. For computerized data, it is possible to have an in-built system for some data checking (e.g. logical and consistency checking). In addition, matching hospital information with HW-collected data for number and identification of cases that arrive directly in the participating hospital, will provide an indirect indication of HW performance in terms of case identification in the field.

9.2 Laboratory data

To ensure correct reading and interpretation of dipstick test results, 5%-10% of systematic random samples of stool specimens can be tested blindly in a reference or supervisory laboratory. In addition, laboratory technicians will be periodically assessed and re-trained in this regard. Logbooks will be maintained by both HWs and the laboratory to check the number of specimens received, specimen identification and time spent between specimen collection and testing.

To ensure the quality of collected data and specimens, the staff involved the in the surveillance as well as in the laboratory are to be trained at the beginning and thereafter periodically, as and when necessary.

10. Ethical considerations

Before one begins any study as mentioned in this protocol, due attention needs to be given to ethical issues involved with different study procedures. For collection of individual and/or family-level data on diarrhoea and relevant non-climate variables, especially for collection of stool specimen, informed consent should be taken from the subject (or from parents or legal guardian if the subject is a minor). Community consent may be sufficient if the plan is not to contact individual subjects, but data are collected from sentinel hospitals and other appropriate records. In any case, it would be very prudent to make the community sufficiently informed about the study and their agreement taken. Maintaining data confidentiality is also of prime importance – wherever necessary, any personally identifiable information must be stripped off before using data for analysis. Hard copies of all forms and records should be kept under strict supervision, limiting access only to appropriate authorities and data handlers. All studies must be formally approved by the appropriate Ethics Committee in the country.

11. Assessing preparedness and response capacity

Since climatic changes can have serious negative impacts on countries (or regions within a country) by increasing diarrhoea occurrences and outbreaks, including changes in pathogen characteristics, all countries should have the capacity for formulating and implementing preparedness and response plans against such threats. It includes a national plan of action that needs to be regularly monitored by a designated authority comprising of people from different sectors, including the private sector wherever appropriate. In the context of climate change and diarrhoeal diseases, regular feedback from an efficient and well-coordinated surveillance system forms the basis of such monitoring. Establishment of sub-regional response centres within a country, and core action committees and facilities for seamless communications among them, would facilitate appropriate and timely action whenever there is an adverse outcome (e.g. an outbreak) or possibility of an impending threat. These centres will maintain contingency stocks of relevant items, including drinking water, halogen tablets, bleaching powder, drugs, vaccines, IV fluids and ORS, with periodic replacements keeping in mind expiry dates. Local health care facilities may be identified to take care of cases during outbreaks and staff therein should be adequately trained to tackle such a situation. In addition, identifying and mitigating factors that negatively influence the climate itself need to be considered for long-term prevention efforts. This also requires periodic monitoring through a coordinated multisectoral approach, which can be strengthened by formulating and implementing relevant laws and regulations. The following table highlights the core activities/items necessary for combating the threats from diarrhoea at different levels of preparedness and response.

Minimum requirements to deal with diarrhoea, climate change and related factors at different levels of preparedness

Level of preparedness	Diarrhoea/Cholera	Climate changes	Factors influencing climate changes
To detect negative impacts on diarrhoea / cholera, including outbreaks.	Continuous surveillance and monitoring system. Efficient data management, report generation and dissemination system. Embedded early warning system to forecast outbreaks. Designated positions / authorities responsible for these activities.	Continuous collection and analysis of climate data. Efficient climate forecast capabilities (short-term or long-term). Established coordination between meteorology and public health departments.	
To combat consequences of diarrhoea / cholera and outbreaks.	Stockpiling of recommended drugs, ORS, vaccines and other supplies. Identification of drug distribution centres in case of emergencies Identification of hospitals / hospital bed reserved for emergencies. Formation of core committees / teams with adequate training.	Construction and maintenance of temporary shelters for displaced people in cases of calamities as a consequence of climate changes.	

Level of preparedness	Diarrhoea/Cholera	Climate changes	Factors influencing climate changes
To prevent (or delay) occurrences of diarrhoea / cholera and climate change.	Provision of safe water supply. Adequate sanitation system. IEC activities to promote hygienic behaviours. Other preventive measures at community levels.		Multisectoral approach involving public health, pollution control, motor vehicles, irrigation and agriculture, finance and planning etc. Established system to disseminate inter-sectoral information and to coordinate appropriate actions. Existence and implementation of appropriate laws / regulations.

12. Outline of the budget

The following is an outline of minimum requirements to carry out different activities for prospective study in a population of 30,000 for one year.

Budget items	No./ Quantity	Cost per unit/month (approx. US$)	Total cost in 12m (approx. US$)	Subtotal (US$)
Personnel:				
Study coordinator	1	750	9000	
Health workers	12	150	1800	
Health assistants (supervisors)	4	275	3300	
Laboratory technician	1	225	2700	
Laboratory attendant	1	150	1800	
Data entry personnel	2	225	2700	
Statistician / Programmer	1	350	4200	
Clerk / Attendant	2	150	1800	
Subtotal				27300
Stationery, including specimen labels			1500	1500
Consumables - General			300	300

Budget items	No./ Quantity	Cost per unit/month (approx. US$)	Total cost in 12m (approx. US$)	Subtotal (US$)
Consumables & test kits - Laboratory				
Specimen containers*	26400	0.25	6600	
Specimen carriage basket	16	10	160	
Cholera dipsticks*	22100	1	22100	
Disposal system			2500	
Lab. furniture & fittings			1500	
Lab. consumables			500	33360
Computing facilities				
Computers with UPS	2	1250	2500	
Printer - Laser	1	650	650	
Storage media for back-up			300	
Furniture, including file cabinets etc			2500	
Internet	1		750	
Software - Antivirus	1	300	300	
Software - Statistical	1	10000	10000	17000
Training, meeting & training materials, SOPs			750	750
Transportation	1	500	6000	6000
Communications		250	3000	3000
Miscellaneous		250	3000	3000
TOTAL				**92210**

*These are only approximate numbers and will vary according to local situations. The calculations will be based on certain assumptions as follows -

Assuming incidence of diarrhoea in total population as 1 episode per person per year, total no. of expected episodes = 30,000; assuming 80% case-capture, total no. of containers required = 24,000 (plus an additional 10% for wastage); assuming 80% of them presenting with loose or watery diarrhoea, no. of cholera dipsticks required = 19,200 (plus additional 15% for wastage and quality control)

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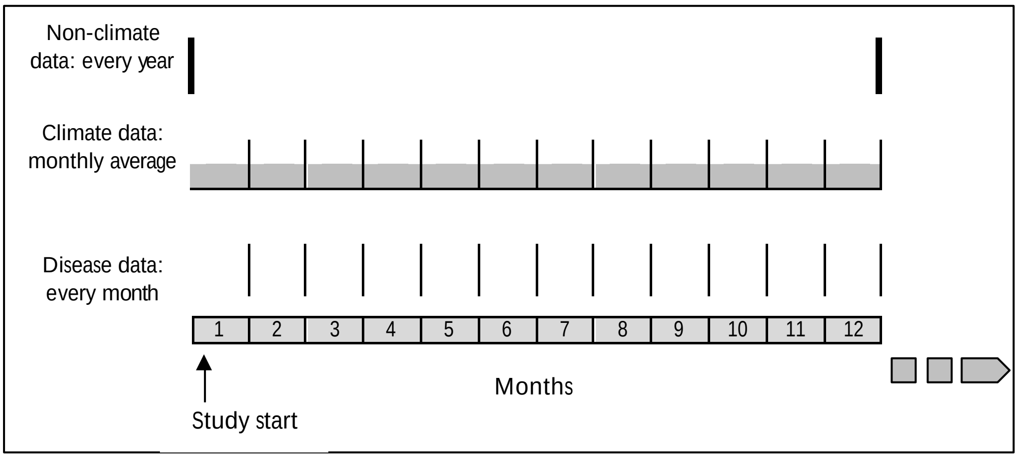
Annex 1

Data collection schedule



Annex 2

Monthly data collection by health workers: information on diarrhoea episodes

Date and time of information collection

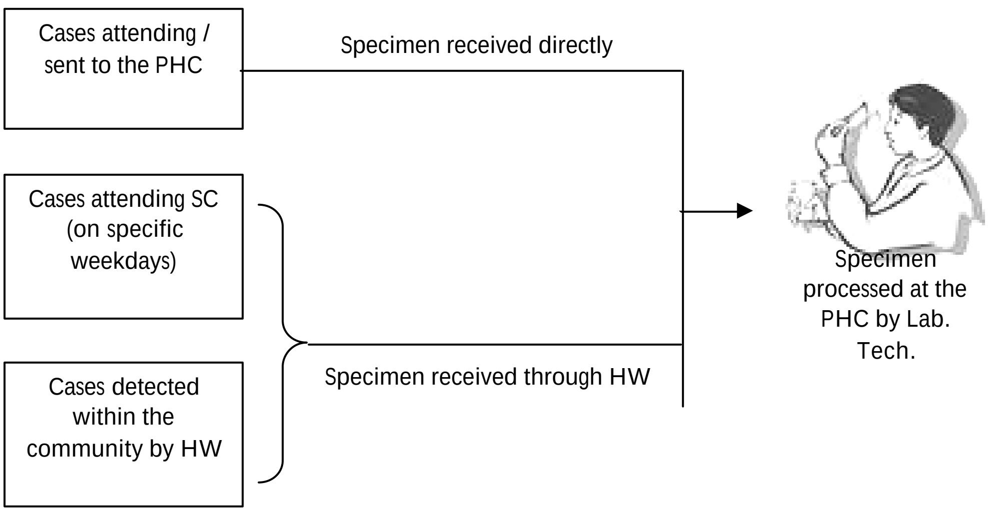
Interviewer name & ID

Sl.No.	Subject ID	Age	Gender (M/F)	Onset of episode		End of episode		Stool character	IV fluid given (Y/N)	Outcome	Specimen collection (Y/N)	Cholera positive (Y/N)
				Date	Time	Date	Time					

Annex 3

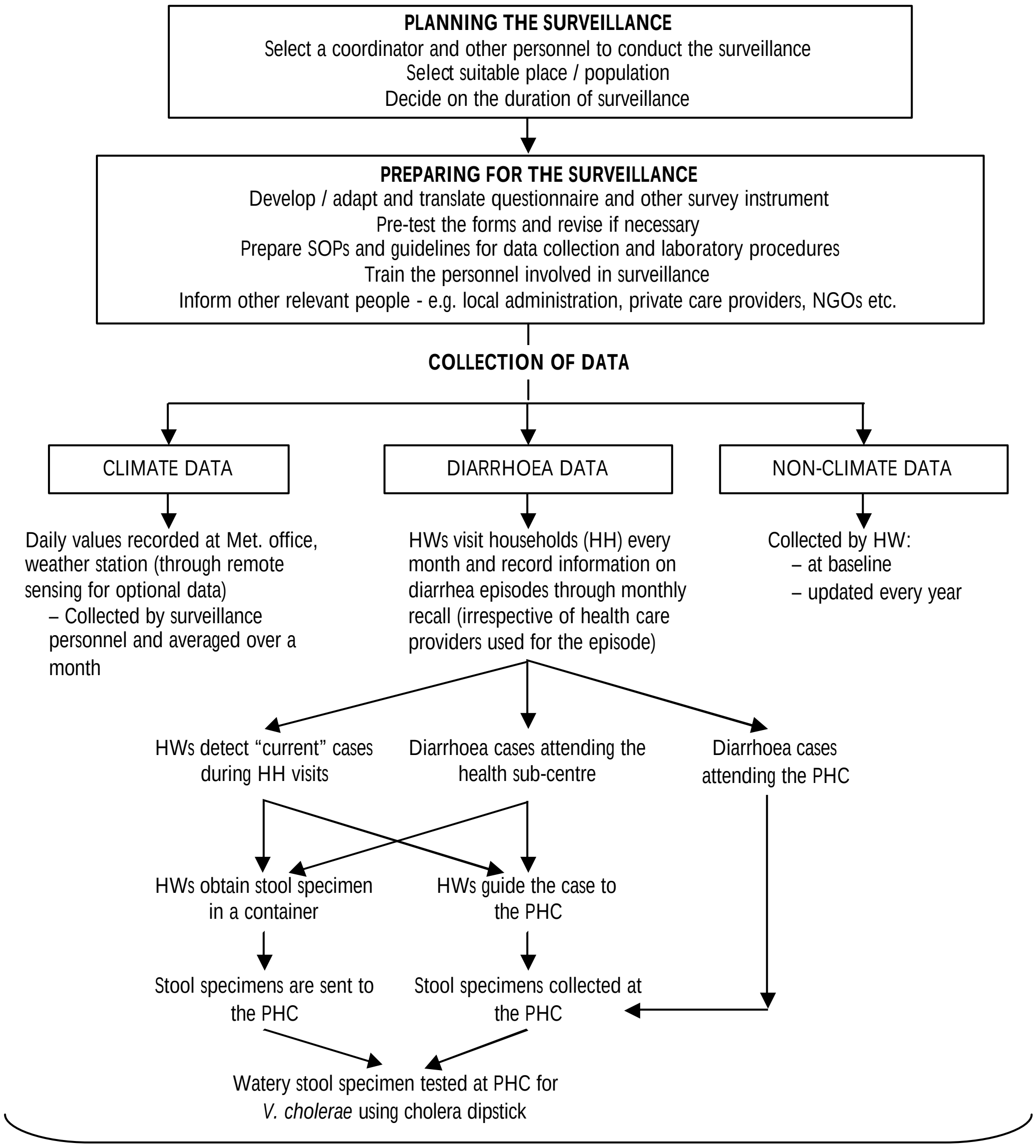
Specimen (stool) collection

Stool specimen (for all acute watery diarrhoea) to test for cholera can be collected at any of the three locations as follows -



Annex 4

Summary of surveillance system



All data forms (including laboratory data) are sent to a central location (PHC / BPHC / other designated place) for computerized data entry and editing. Periodic feedback on data quality will be given to authorized persons for appropriate action. Periodic training will be given to all field and laboratory persons to maintain quality of data collection.

Climate change, if it occurs at the level projected by current global models, may have important and far-reaching effects on infectious diseases, especially those that are transmitted by poikilothermic arthropods such as mosquitoes and ticks. Climate change is also expected to affect acute diarroheal diseases. This generic research protocol deals with prospective studies to assess the negative health impact of climate change on diarrhoeal diseases with special emphasis on cholera.

World Health Organization
Regional Office for South-East Asia
World Health House
Indraprastha Estate,
Mahatma Gandhi Marg,
New Delhi-110002, India

SEA-CD-207