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Challenges in developing methods for quantifying the effects of weather and climate on water-associated diseases: A systematic review

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Abstract

Infectious diseases attributable to unsafe water supply, sanitation and hygiene (e.g. Cholera, Leptospirosis, Giardiasis) remain an important cause of morbidity and mortality, especially in low-income countries. Climate and weather factors are known to affect the transmission and distribution of infectious diseases and statistical and mathematical modelling are continuously developing to investigate the impact of weather and climate on water-associated diseases. There have been little critical analyses of the methodological approaches. Our objective is to review and summarize statistical and modelling methods used to investigate the effects of weather and climate on infectious diseases associated with water, in order to identify limitations and knowledge gaps in developing of new methods. We conducted a systematic review of English-language papers published from 2000 to 2015. Search terms included concepts related to water-associated diseases, weather and climate, statistical, epidemiological and modelling methods. We found 102 full text papers that met our criteria and were included in the analysis. The most commonly used methods were grouped in two clusters: process-based models (PBM) and time series and spatial epidemiology (TS-SE). In general, PBM methods were employed when the bio-physical mechanism of the pathogen under study was relatively well known (e.g. Vibrio cholerae); TS-SE tended to be used when the specific environmental mechanisms were unclear (e.g. Campylobacter). Important data and methodological challenges emerged, with implications for surveillance and control of water-associated infections. The most common limitations comprised: non-inclusion of key factors (e.g. biological mechanism, demographic heterogeneity, human behavior), reporting bias, poor data quality, and collinearity in exposures. Furthermore, the methods often did not distinguish among the multiple sources of time-lags (e.g. patient physiology, reporting bias, healthcare access) between environmental drivers/
exposures and disease detection. Key areas of future research include: disentangling the complex effects of weather/climate on each exposure-health outcome pathway (e.g. person-to-person vs environment-to-person), and linking weather data to individual cases longitudinally.

Author summary

Unsafe water supplies, limited sanitation and poor hygiene are still important causes of infectious disease (e.g. Cholera, Leptospirosis, Giardiasis), especially in low-income countries. Climate and weather affect the transmission and distribution of infectious diseases. Therefore, scientists are continuously developing new analysis methods to investigate the impacts of weather and climate on infectious disease, and particularly, on those associated with water. As these methods are based on an imperfect representation of the real world, they are inevitably subjected to many challenges. Based on a systematic review of the literature, we identified seven important challenges for scientists who develop new analysis methods.

Introduction

The seasonal and geographic distributions of infectious diseases are currently among the best indications of an association with weather and climate. The literature on climate effects is expanding in response to concerns about global climate change. The significance of the methods and data available is not only confined to the technical procedural aspects; methods and data also impact on the formulation of the specific scientific questions, their selection, and the development of hypotheses. Although our understanding of how weather and climate affect diseases has improved, the wide range of research methods applied make it difficult to get a robust overview of the state of research.

The relationship between climate/weather and infectious diseases is complex (e.g.[1]), as shown in the example illustrated in Fig 1. Investigating the effects of weather and climate on infectious diseases requires the ability to: i) disentangle concurrent modes of transmissions (e.g. environmental from human-to-human transmission); ii) tease apart the individual effects of multiple exposures at different temporal and spatial scales; iii) identify and separate socioeconomic drivers and behavioural causes; iv) integrate all these different processes into a unified perspective; v) attribute changes in disease to observed environmental changes (such as climate change); and vi) quantify infectious disease burden resulting from current social, economic and environmental conditions which can help to project the future disease burden resulting from these changes. These are difficult methodological and conceptual demands, and the scientific and public health community could benefit from a critical overview of the available research methods and the challenges ahead.

In this paper, we focus on the particularly important, especially in developing countries, class of infectious diseases associated with water (including those classified as neglected tropical diseases (NTD) according to the World Health Organisation (WHO) [2] the US Centers for Disease Control and Prevention (CDC) [3]) and the journal Plos NTD [4]) (Table 1). According to WHO estimates, 1.1 billion people globally drink water that is of at least ‘moderate’ risk of faecal contamination [5], and 842,000 annual deaths are attributable to unsafe
Fig 1. Illustration of the steps and potential pathways from being exposed to the pathogen reservoir to detection of disease. The red (blue) taps and swimmers represent contaminated (uncontaminated) drinking and recreational water. The red (blue) silhouette represents infected (not-infected) humans. Here and throughout, any kind of environment-containing pathogens that can serve as a medium for transmission (e.g. drinking water, sewage system) is referred to as “pathogen reservoir”; any form of direct or indirect contact with such medium, irrespective of the presence of the pathogen, is referred to as an “exposure”. According to this conceptual scheme, a disease-free situation is the combination of negligible pathogen...
Infectious diseases associated with water are classified as follows: “water-system-related” infections (i.e. via aerosols from poorly managed cooling systems, e.g. Legionellosis), “water-based” infections (i.e. via aquatic vectors or intermediate in hosts, e.g. Schistosomiasis), “water-borne” infections (i.e. via bacterial, parasitic and viral oral-faecal infection through ingestion, e.g. cholera), and “water-washed” infections (i.e. infections arising from poor hygiene due to insufficient water, these can also include oral-faecal infection, e.g. hookworm) [8] (see Table 1). Here and throughout, we use the expression “water-associated” to refer to these latter classes of diseases. Of note, we excluded diseases arising from ingestion/contact with inorganic and other chemical compounds (e.g. arsenic) and vector-borne infections linked with water (e.g. malaria, rift valley fever, river blindness) from the “water-associated” diseases.

This Review is not a prescriptive guideline of available methods for a range of problems. We reviewed and summarised the methods used to investigate the effects of weather and climate on infectious diseases associated with water, with the objective of identifying the challenges that scientists are facing when develop new analysis methods. We focused on quantitative analytical approaches, such as: mathematical models, statistical analysis, computational techniques, numerical simulations, epidemiological models and computer-generated agent based models. We excluded purely descriptive observational studies [9].

Discriminating between studies which build explanatory models versus create predictive models is particularly important in statistical modelling [10]. We however avoided this way of grouping. The dichotomy explanatory vs predictive models might be clear from an epistemological point of view [10], nevertheless, we have found it really challenging to rigorously separate papers according to this classification. For most papers, a formal distinction is often impossible as the causal relationships are inferred/discussed from the patterns captured from predictive models, and vice versa the hypothetical-deductive models (e.g. driven by causal relationships), could both be able to predict a range of future scenarios.

Methods

Search strategy, selection criteria and methods

The methods for the systematic review followed the Guidelines developed by the Cochrane Collaboration [11]. We searched for English language articles published from 2000 to April 2015. The following databases were searched: Scopus, Medline, EMBASE, CINAHL, Cochrane Library, Global Health and LILACS bibliographic databases. The literature after April 2015 was also monitored using a daily email alert tool provided by Google Scholar (searching for “water borne disease” and “water related disease”) to identify potential papers adopting newly-developed methods not covered by the initial search.

We used search terms related to water-associated diseases (e.g. “water transmission” OR “contaminated fresh water” OR “unsafe water supply” etc.) and quantitative methodologies (e.g. “mathematical epidemiology” OR “simulation”) and weather and climate. The full list of
Table 1. Organisms causing diseases related to water (excluding vector borne diseases). The symbol ● specifies the known routes of transmission (not exclusively); (●) specifies the probable route of transmission but no direct evidence available. The last column indicates which organism is classified as Neglected Tropical disease, according to the World Health Organisation (W) [2], the Centers for Disease Control and Prevention (C) [3], and the journal PLOS Neglected Tropical Diseases (P) [4]. The different routes of transmission are: A) Drinking water borne; B) Water washed (reduced water access); C) Water based; D) Foodborne through water; E) Water infecting wounds; F) Bathing water transmission; G) Respiratory waterborne; H) Toxic poisoning through a bloom; I) Infection or disease related to damp; J) Medical water or solutions.

| Organism               | Routes of Transmission | Organism type | Details of disease & organism & water relationship | Classified as Neglected Tropical Disease |
|------------------------|------------------------|---------------|----------------------------------------------------|----------------------------------------|
|                        | A)                     | B)            | C)        | D)        | E)        | F)        | G)        | H)        | I)        | J)        |                         |
| Drinking water-borne   | ●                      | ●             | ●         | ●         |           |           |           |           |           |           | Protozoan               |
|                        |                        |               |           |           |           |           |           |           |           |                        | Primary amoebic meningoencephalitis, eye infections |
| Adenovirus             | ●                      |               |           | ●         |           |           |           |           |           |           | Virus                   |
|                        |                        |               |           |           |           |           |           |           |           |                        | Diarrhoea; respiratory infection |
| Alexandrium spp.       | ●                      | ●             | ●         |           |           |           |           |           |           |           | Dinoflagellate          |
|                        |                        |               |           |           |           |           |           |           |           |                        | Shellfish poisoning from bioaccumulation |
| Alternaria spp.        | ●                      |               | ●         |           |           |           |           |           |           |           | Fungus                  |
|                        |                        |               |           |           |           |           |           |           |           |                        | Alimentary toxic aleukia associated with mouldy grain crops |
| Anabena spp.           | ●                      |               | ●         |           |           |           |           |           |           |           | Cyanobacteria           |
|                        |                        |               |           |           |           |           |           |           |           |                        | Exposure to contaminated dialysis, drinking and bathing water |
| Ancylostoma spp.       | (●)                    |               | ●         |           |           |           |           |           |           |           | Roundworm               |
|                        |                        |               |           |           |           |           |           |           |           |                        | Hookworm infection WP |
| Angiostrongylus spp.   | ●                      | ●             | ●         |           |           |           |           |           |           |           | Roundworm               |
|                        |                        |               |           |           |           |           |           |           |           |                        | Larvae develop in aquatic animals WCP |
| Anisakis spp.          | ●                      | ●             | ●         |           |           |           |           |           |           |           | Roundworm               |
|                        |                        |               |           |           |           |           |           |           |           |                        | Lifecycle in fish W |
| Aphanizomenon spp.     | ●                      |               | ●         |           |           |           |           |           |           |           | Cyanobacteria           |
|                        |                        |               |           |           |           |           |           |           |           |                        | Exposure to contaminated dialysis, drinking and bathing water |
| Arcobacter spp.        | (●)                    |               | ●         |           |           |           |           |           |           |           | Bacteria                |
|                        |                        |               |           |           |           |           |           |           |           |                        | Contamination of drinking water |
| Ascaris lumbricoides   | ●                      |               |           |           |           |           |           |           |           |           | Roundworm               |
|                        |                        |               |           |           |           |           |           |           |           |                        | Drinking water contaminated by nightsoil WCP |
| Aspergillus spp.       | ●                      |               |           |           |           |           |           |           |           |           | Fungus                  |
|                        |                        |               |           |           |           |           |           |           |           |                        | Linked to Balkan endemic nephropathy from mouldy grain |
| Astrovirus             | ●                      |               |           |           |           |           |           |           |           |           | Virus                   |
|                        |                        |               |           |           |           |           |           |           |           |                        | Contamination of drinking water |
| Baylisascaris procyonis| ●                      |               |           |           |           |           |           |           |           |           | Roundworm               |
|                        |                        |               |           |           |           |           |           |           |           |                        | Infection from racoons through water? WP |
| Burkholderia pseudomallei| ●                     | ●             | ●         |           |           |           |           |           |           |           | Bacteria                |
|                        |                        |               |           |           |           |           |           |           |           |                        | Parasite contamination through untreated drinking water |
| Burkholderia cepacia   | ●                      |               |           |           |           |           |           |           |           |           | Bacteria                |
|                        |                        |               |           |           |           |           |           |           |           |                        | Possible water transmission |
| Balamuthia mandrillaris| ●                      | ●             |           |           |           |           |           |           |           |           | Protozoa                |
|                        |                        |               |           |           |           |           |           |           |           |                        | Parasite contamination through untreated soil/ water P |

(Continued)
| Organism Type | Organism | Routes of Transmission | Details of disease & organism & water relationship |
|--------------|----------|------------------------|--------------------------------------------------|
| Bacteria     | Campylobacter jejuni | Drinking water-borne | Contamination of unchlorinated drinking water |
|              | Chlamydia trachomatis | Infection related to damp | Transmission through flies as a result of lack of water to wash |
|              | Clostridium botulinum | Respiratory water-borne | Botulism in injecting drug users; Washwater contaminating cans |
|              | Cryptosporidium spp. | Drinking water-borne | Contamination of drinking water |
|              | Diphyllobothrium latum | Food-borne through water | Infection through uncooked fish |
|              | Dracunculus medinensis | Water-borne | Contamination of drinking water containing copepods |
|              | E. coli | Drinking water-borne | Contamination of drinking water |
|              | Helicobacter pylori | Drinking water-borne | Contamination of drinking water |
|              | Plasmodium falciparum | Drinking water-borne | Contamination of drinking water |
|              | Serratia marcescens | Water-borne | Contamination of drinking water |
|              | Shigella flexneri | Drinking water-borne | Contamination of drinking water |
|              | Vibriosis | Drinking water-borne | Contamination of drinking water |
|              | Vibrio cholerae | Drinking water-borne | Contamination of drinking water |
|              | Vibrio parahaemolyticus | Drinking water-borne | Contamination of drinking water |
|              | Vibrio vulnificus | Drinking water-borne | Contamination of drinking water |
|              | Yersinia enterocolitica | Drinking water-borne | Contamination of drinking water |

Table 1. (Continued)

Challenges with methods for water-associated disease
| Organism | Routes of Transmission | Organism type | Details of disease & organism & water relationship | Classified as Neglected Tropical Disease |
|----------|------------------------|---------------|-------------------------------------------------|-------------------------------------|
| Echinococcus spp. | Drinking water-borne, Water washed (reduced water access) | Flatworm | Transmission through water consumption | WCP |
| Echinostoma spp. | Drinking water-borne, Water-based | Flatworm | Infection through consumption of uncooked molluscs or amphibians | WP |
| Encephalitozoon spp. | Drinking water-borne | Fungus | Parasite contamination through untreated drinking water | |
| Entamoeba histolytica | Drinking water-borne | Protozoa | Diarrhoea, dysentery & abscess | P |
| Enterobius vermicularis | Drinking water-borne | Roundworm | Parasite contamination through untreated drinking water | |
| Enterocytozoon bieneusi | Drinking water-borne | Fungus | Parasite contamination through untreated drinking water | |
| Enteroviruses including ECHO coxsackie, polio etc. | Drinking water-borne | Virus | Sewage contamination of drinking water | |
| E. coli O157 & others | Drinking water-borne | Bacteria | Contamination of drinking water | P |
| Enteropathogenic (EPEC) | Drinking water-borne | Bacteria | Contamination of drinking water | P |
| enterotoxigenic (ETEC) | Drinking water-borne | Bacteria | Contamination of drinking water | P |
| Enteroinvasive (EIEC) | Drinking water-borne | Bacteria | Contamination of drinking water | P |
| Fasciola gigantica | Drinking water-borne | Flatworm | Infection through contaminated aquatic plants | WCP |
| Fasciola hepatica | Drinking water-borne | Flatworm | Infection through contaminated aquatic plants | WCP |
| Fasciolopsis buski | Drinking water-borne | Flatworm | Infection through contaminated aquatic plants | WCP |
| Fusarium spp. | Drinking water-borne | Fungus | Implicated in alimentary toxic aleukia. | |
| Gambierdiscus spp. | Drinking water-borne | Dinoflagellate | Ciguatera fish poisoning from bioaccumulation | |
| Giardiasp. | Drinking water-borne | Protozoa | Contamination of drinking and recreational water | P |

(Continued)
| Organism                  | Routes of Transmission | Organism type | Details of disease & organism & water relationship | Classified as Neglected Tropical Disease |
|--------------------------|------------------------|---------------|--------------------------------------------------|------------------------------------------|
|                          | A) B) C) D) E) F) G) H) I) J) |               |                                                  |                                          |
| Drinking water-borne     |                        |               |                                                  |                                          |
| Water washed (reduced water access) |                        |               |                                                  |                                          |
| Water-based              |                        |               |                                                  |                                          |
| Food-borne through water |                        |               |                                                  |                                          |
| Water infecting wounds   |                        |               |                                                  |                                          |
| Bathing water            |                        |               |                                                  |                                          |
| Respirat. water-borne    |                        |               |                                                  |                                          |
| Toxic poisoning through a bloom |                        |               |                                                  |                                          |
| Infection or disease related to damp |                        |               |                                                  |                                          |
| Medical water or solutions |                        |               |                                                  |                                          |
| **Gnathostoma spp**      | ●                      | Roundworm     | Transmission through eating uncooked fish or frogs | W                                        |
| **Gongylonema pulchrum** | ●                      | Roundworm     | Rare infection linked to water consumption       | WP                                       |
| **Gonyaulax tamarensis** | ● ●                    | Dinoflagellate| Ciguatera fish poisoning from bioaccumulation    |                                          |
| **Gymnodinium spp.**     | ● ●                    | Dinoflagellate| Shellfish poisoning from bioaccumulation         |                                          |
| **Helicobacter pylori**  | ●                      | Bacteria      | Transmission by water in developing countries   |                                          |
| **Hepatitis A**          | ●                      | Virus         | Contamination of unchlorinated drinking water   |                                          |
| **Hepatitis E**          | ●                      | Virus         | Contamination of unchlorinated drinking water   |                                          |
| **Heterophyes heterophyes** | ● ●                   | Flatworm      | Infection from uncooked fish                    | WP                                       |
| **Isospora belli**       | ●                      | Protozoa      | Parasite contamination through untreated drinking water |                                          |
| **Karenia spp.**         | ● ●                    | Dinoflagellate| Shellfish poisoning from bioaccumulation         |                                          |
| **Legionella pneumophila** | ● ●                   | Bacteria      | Contamination of warm water systems in buildings |                                          |
| **Leptospira spp.**      | ● ● ● ●                | Bacteria      | Water contamination from wild and agricultural animals | P                                    |
| **Lyngeya majuscula**    | ● ● ● ●                | Cyanobacteria | Contact exposure to algae                        |                                          |
| **Microcystis aeruginosa** | ● ● ● ●             | Cyanobacteria | Exposure to contaminated dialysis, drinking and bathing water |                                          |
| **Mycobacterium avium**  | ● ● ● ●                | Bacteria      | Contamination of water systems                  |                                          |
| **M. avium** Paratuberculosis | ● ● ● ●             | Bacteria      | Natural water and food contaminated by cow and sheep faeces |                                          |
| **Mycobacterium chelonae** | ● ● ● ●             | Bacteria      | Contamination of water systems                  |                                          |
| **Mycobacterium fortuitum** | ● ● ● ●             | Bacteria      | Contamination of water systems                  |                                          |
| **Mycobacterium marinum** | ● ● ● ●                | Bacteria      | Contaminated fish tanks                         |                                          |
| Organism                  | Routes of Transmission | Organism type | Details of disease & organism & water relationship | Classified as Neglected Tropical Disease |
|--------------------------|------------------------|---------------|---------------------------------------------------|------------------------------------------|
| **Mycobacterium ulcerans** | A) B)                  | Bacteria      | Wound infections with contamination from water plants | WCP                                      |
| **Naegleria fowleri**    | C)                     | Protozoa      | Contamination of natural thermal waters           |                                          |
| **Nanophyetus salmincola** | D) E)                 | Flatworm      | Infection from uncooked fish                      | W                                         |
| **Necator americanus**   | F)                     | Roundworm     | Infection from soil or water                      | WCP                                      |
| **Nitzschia navis-yaeringica** | G) H) J)          | Diatom        | Shellfish poisoning from bioaccumulation          |                                          |
| **Nodularia spumigena**  | I)                     | Cyanobacteria | Exposure to contaminated dialysis, drinking and bathing water |                                          |
| **Norovirus**            | J)                     | Virus         | Contamination of unchlorinated drinking water     |                                          |
| **Ophisthorchis spp.**   |                        | Flatworm      | Infection from uncooked fish                      | WP                                       |
| **Oscillatoria spp.**    |                        | Cyanobacteria | Exposure to contaminated dialysis, drinking and bathing water |                                          |
| **Ostreopsis spp.**      |                        | Dinoflagellate| Respiratory exposure to algal blooms              |                                          |
| **Paragonimus spp.**     |                        | Flatworm      | Infection from uncooked crabs                     | WP                                       |
| **Penicillium spp.**     |                        | Fungus        | Toxins implicated in Balkan endemic nephropathy and alimentary toxic aleukia. |                                          |
| **Phormidium favosum**   |                        | Cyanobacteria | Exposure to contaminated dialysis, drinking and bathing water |                                          |
| **Plesiomonas shigelloides** |                        | Bacteria      | Contamination of natural waters                  |                                          |
| **Procentrum spp.**      |                        | Dinoflagellate| Shellfish poisoning from bioaccumulation          |                                          |
| **Protoperidinium crassipes** |                        | Dinoflagellate| Shellfish poisoning from bioaccumulation          |                                          |
| **Pseudomonas aeruginosa** |                        | Bacteria      | Ear, eye and skin infections from bathing and other waters |                                          |
| **Pseudo-nitzschia spp.** |                        | Diatom        | Shellfish poisoning from bioaccumulation          |                                          |
| Organism                   | Routes of Transmission | Organism type | Details of disease & organism & water relationship | Classified as Neglected Tropical Disease |
|---------------------------|------------------------|---------------|---------------------------------------------------|------------------------------------------|
| **Table 1.** (Continued)  |                        |               |                                                   |                                          |
| **A)** Drinking water-borne | **B)** Water washed (reduced water access) | **C)** Food-borne through water | **D)** Water infecting wounds | **E)** Bathing water | **F)** Respirat. water-borne | **G)** Toxic poisoning through a bloom | **H)** Infection or disease related to damp | **I)** Medical water or solutions |               |
| **Pseudoterranova spp.**  | ●                      | ●             |                                                   | Roundworm Infection through consuming raw fish | WP                                      |
| **Pyrodinium spp.**       | ●                      | ●             |                                                   | Dinoflagellate Shellfish poisoning from bioaccumulation |                                        |
| **Rhinosporidium seeberi** | ●                      | ●             |                                                   | Protozoa Infection linked to bathing and washing |                                        |
| **Rotavirus**             | ●                      |               |                                                   | Virus Contamination of drinking water     |                                        |
| **Stenotrophomonas maltophilia** |               |               |                                                   | Bacteria Contaminated hospital water systems |                                        |
| **Salmonella spp.**       | ●                      |               |                                                   | Bacteria Contamination of untreated drinking water | P                                      |
| **Salmonella Typhi & Paratyphi** | ●              |               |                                                   | Bacteria Contamination of untreated drinking water | P                                      |
| **Schistosoma intercalatum** | ●                    | ●             |                                                   | Flatworm Infection through the skin from working or bathing in water | WCP                                    |
| **Schistosoma haematobium** | ●                    | ●             |                                                   | Flatworm Infection through the skin from working/ bathing in water | WCP                                    |
| **Schistosoma mansoni**   | ●                      | ●             |                                                   | Flatworm Infection through the skin from working/ bathing in water | WCP                                    |
| **Schistosoma mekongi**   | ●                      | ●             |                                                   | Flatworm Infection through the skin from working/ bathing in water | WCP                                    |
| **Schistosoma spindale**  | ●                      | ●             |                                                   | Flatworm Infection through the skin from working/ bathing in water | WCP                                    |
| **Sapovirus**             | ●                      |               |                                                   | Virus Contamination of untreated drinking water |                                        |
| **Sarcocystis hominis**   | ●                      |               |                                                   | Protozoa Contamination of natural waters with dog faeces |                                        |
| **Shigella spp.**         | ●                      | ●             |                                                   | Bacteria Contamination of untreated drinking and bathing water | P                                      |
| **Spirillum minus**       | ●                      |               |                                                   | Bacteria Potable water contaminated by rodents |                                        |
| **Spirometra spp.**       | ●                      | ●             |                                                   | Flatworm Sparganosis infection from copepods in drinking water | WCP                                    |
| **Taenia solium**         | ●                      |               |                                                   | Flatworm Ova of T. solium can cause cysticercosis through ingestion in drinking water | WCP                                    |
| Organism                          | Routes of Transmission | Organism type | Details of disease & organism & water relationship                                                                 | Classified as Neglected Tropical Disease |
|----------------------------------|------------------------|---------------|---------------------------------------------------------------------------------------------------------------|------------------------------------------|
| **Trichodesmium erythraeum**     | B)                     | Cyanobacteria | Exposure to contaminated dialysis, drinking and bathing water                                                 | WCP                                      |
| **Trichuris trichiura**          |                         | Protozoa      | Can be transmitted through drinking water                                                                     |                                          |
| **Toxocara canis**               | (●)                    | Roundworm     | Possible transmission from contaminated soil and water                                                        | P                                        |
| **Toxoplasma gondii**            | ●                      | Protozoa      | Infection through oocyst contamination of drinking water                                                      |                                          |
| **Trichobilharzia regenti**      | ●                      | Flatworm      | Infection through the skin from working/bathing in water                                                      | WP                                       |
| **Uncinaria spp.**               | (●)                    | Roundworm     | Larva migrans. Oral transmission through water likely                                                          | W                                        |
| **Vibrio cholerae**              | ●●                     | Bacteria      | Transmission from estuarine, human and food sources                                                            | P                                        |
| **Vibrio parahaemolyticus**      | ●●                     | Bacteria      | Contamination of shellfish                                                                                     |                                          |
| **Vibrio vulnificus**            | ●●                     | Bacteria      | Contamination of shellfish                                                                                     |                                          |
| **Vibrio spp. (non-V. cholerae)**| ●                      | Bacteria      | Contamination of shellfish                                                                                     |                                          |
| **Yersinia enterocolitica**      | ●                      | Bacteria      | Contamination of untreated water by rodents                                                                    |                                          |
| **Yersinia pseudotuberculosis**  | ●                      | Bacteria      | Contamination of untreated water by rodents                                                                    |                                          |

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search terms is in the Supporting Information, S2 Text. Papers were reviewed by two people (GL and GN). As the pool of returned papers was quite large, we decided to not use additional specific search terms for pathogens (e.g. ’cholera’, ’rotavirus’) or diagnosis/symptoms (e.g. ’diarrhoea’, ’gastroenteritis’), as this would require a subjective list of potential pathogens and introduce unnecessary bias in the selection of the papers. We included articles that: i) were published in peer reviewed journals; ii) included an infectious disease in human beings; and iii) developed new methods and/or applied established methods to investigate the effects of weather and/or climate on infectious diseases (including papers for which weather and climate variables were among other equally important factors driving disease transmission).

The final set of papers was archived in EndNote (see Supporting Information, S1 Table). We identified specific questions related to the nature of the methods, their range, applicability and limitations (Table 2) that we wanted the Review to address. We then created a spreadsheet consisting of records (rows) corresponding to each paper in our final database, and columns to address the specific questions. Analysis was done in R open source analytic software [12].

Papers were clustered according to the methodology used. More precisely, for each paper we identified the list of technical keywords associated with the methods, including both general concepts (e.g. “time series analysis”) and sub-analysis terms (e.g. “partial autocorrelation function”); the full list of technical keywords is presented in the Supporting Information, S1 Table. Papers that share the same keyword are often connected. Consequently, analytical

| Table 2. List of scientific questions and related notes. |
|---------------------------------------------------------|
| Questions                                               |
|                                                         |
| 1) What are the main water-related pathogens investigated and where do they occur? |
| Estimate the number of studies for each disease/ pathogens under investigation. Ascertain the countries where the disease occurred. |
| 2) What methods have been used?                         |
| Ascertain the key epidemiological methods developed and used so far. Classify the methods in terms of general approaches: such as descriptive phenomenology, process based models (e.g. mechanistic compartmental models or agent based models), statistical analysis of empirical data (e.g. time series analysis) etc. |
| 3) Is the method applied to investigate the effect of climate change or weather or both? |
| Assess if the method is actually or potentially applied to climate change and/or weather |
| 4) Does the type of method depend on the disease/pathogen under investigation? |
| 1. Ascertain if there is a preferential use of the methods towards particular disease/pathogen and identify possible explanations |
| 5) What are other key features of the methods?           |
| Identify the specific environmental factors that the method is focusing on (e.g. temperature and rainfall). Ascertain if the method take into account: |
| 1. Temporal variations (e.g. seasonalties and El Niño weather cycles) |
| 2. Evolution of pathogen |
| 3. Human behaviour and/or social and political scenarios (e.g. national economic factors, conflicts, food production, human mobility, demography etc.) |
| 4. Any kind of heterogeneity (e.g. spatial variation, age group, household income) |
| An explicit model for the pathogen dynamic in the reservoir |
| 6) How were the results assessed?                        |
| Establish if and how the method has been validated |
| 7) What are the limitations of the method according to the authors? |
| Describe the limitations of the methods identified by the authors |

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methods that are likely to be used together in the same papers tend to cluster. Analysis was done by using the “igraph” package in R [13].

Results

Overall, 102 papers were included in the analysis (Fig 2). Analysis of the findings and synthesis of the challenges in formulating new methods are summarised below.

Analysis: Seven particular scientific questions addressed by the review

1) What are the main water-associated pathogens investigated and where do they occur?  Fig 3 shows the frequency of pathogens in the final set of papers. *Vibrio cholerae* has been studied most for climate and weather effects. A significant proportion (approximately 20% of papers) focused on unspecified water-associate pathogens and these studies were mostly theoretical process-based models. The next significant categories of studies were papers that looked at diarrheal illness as a broad category based on health service data that did not include pathogen-specific information. In terms of pathogen-specific outcomes, the following pathogens were most studied (after *Vibrio cholerae*): Cryptosporidium spp., *Leptospira* spp., *Schistosoma* spp. *Giardia* sp. and *Salmonella* spp. Many of these are classified as NTD [2–4].

Fig 4 shows the countries where the studies were based. A good proportion of these theoretical process-based models did not link their study with any data for diseases occurring in a particular country (therefore, the outcome was listed as “General” in Fig 4). The country with the most studies (about 10% of papers) was Bangladesh, mostly in relation to cholera, followed by studies on disease data collected in US, China and Canada (Fig 4).

Thus, the pathogens reported in these studies reflect geographic (origin of infections) and socio-economic (quality of data) features: studies on cholera were associated with low and middle income countries, while *Cryptosporidium* spp. and *Campylobacter* spp. were more likely reported in high income countries that have good laboratory-based passive surveillance systems (Fig 4).

2) What methods have been used?  The set of all technical keywords describing the methods used in at least two papers is displayed in a keyword network in Fig 5 (a high-resolution image for the methods used in each paper can be found in the Supporting Information, S1 Fig, see also S1 Table). The figure suggests that the most commonly used methods can be grouped into two main clusters:

- **Process-Based Models** (PBM), which are typically described by mechanistic compartmental models [14],

- **Time series and spatial epidemiology** (TS-SE) such as time series and regression analysis [15] and spatial methods typically based on geographic information system (GIS) [16].

These clusters can overlap. For examples, instances of spatial compartmental models have been developed.

Fig 5 is perhaps the most objective way of representing the methods used in the reviewed papers as it is based simply on the technical keywords recorded by their authors. As the technical keywords can be very specific, the next exercise was to identify the general methods used in the papers. A list of the most common general methods is shown in Fig 6 and in S1 Table in the Supporting Information. The entries in Fig 6 and S1 Table do not reflect an established”-taxonomy” of the methods (which is not available in the literature); they are mainly guided by the patterns which emerged from keyword network (Fig 5) and selected based on their
24,943 search results based on concepts of water-associated risk, weather and climate exposures, and a range of quantitative methods.

| Database       | English | Non-English | Conference Abstracts | Total  | Duplicates |
|----------------|---------|-------------|----------------------|--------|------------|
| Medline        | 8,062   | 462         | 0                    | 8,514  | 2,963      |
| Embase         | 11,468  | 345         | 1,387                | 13,200 | 1,877      |
| CINAHL         | 231     | 0           | 0                    | 231    | 36         |
| Global Health  | 2,657   | 0           | 249                  | 2,906  | 591        |
| LILACS         | 23      | 0           | 0                    | 23     | 4          |
| SCOPUS         | 68      | 1           | 0                    | 69     | 0          |
| Total          | 22,509  | 798         | 1,636                | 24,943 | 5,461      |

No Duplicates 17,048 665 1,474 19,482

17,048 abstracts were stored in EndNote®. By using EndNote search tool, the list of abstracts was further filtered to select documents focusing on water-associated infectious diseases only.

7,895 excluded
5,461 Duplicates
1,636 Conference Abstracts
798 Non-English

15,518 excluded
Most of these documents investigated risk and hazard associated with water (e.g. hurricanes, flood, inorganic pollutant) of non-pathogenic nature.

1530 abstracts from systematic search

1547 abstracts were reviewed in total 1530 from the search plus 17 abstracts already known to the authors (in the next step, 3 of the 17 abstracts were excluded after reading the full text)

1,331 excluded
324 not infectious diseases; 1007 no use of quantitative methods and/or no study of the effect of weather/climate on infectious disease. For 12 of these papers the full text not available

204 full text review

102 excluded
No use of quantitative methods and/or no study of the effect of weather/climate on infectious disease.

102 studies included

Fig 2. Flow chart describing the selection process of all abstracts.

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potential relevance for the study of the effects of weather and climate. For example, a close inspection of Fig 5 suggests that a substantial number of papers in the PBM clusters employed “Dose-Response Model” (which often use environmental variables, such as temperature as inputs); we therefore identified “Models comprising Exposure-Response Relationship” as a general method.

The same principle guided the structure of Table 3, which presents some key features of the clusters of methods. In Table 3, however, we did not discuss methods such as “Descriptive Statistics” and “Survey/Surveillance/Sampling” since these were too generic in terms of their use...
Fig 4. (a) Distribution of countries for which water-associated disease data were the focus of the reviewed papers (b) Geographic
distribution of the 7 most commonly studied water-associated pathogens (resulting either in an epidemic or endemic situations) which were
the focus of the reviewed papers. Each circle refers to specific countries, In particular, the largest circle in Asia, refers to Bangladesh.

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Fig 5. Cluster analysis of methods. Each dot corresponds to a reviewed paper; the brown bubbles correspond to the keywords describing the techniques. A connection between a paper and a keyword occurs when the related technique is used. The size of the bubble increases (logarithmically) with the number of papers citing the keyword. For visual purpose only, i) the bubbles are displayed with different shades of brown and ii) the technical keywords (listed in S1 Table in the Supporting Information) describing methods used by only one paper are not displayed (the full set is shown in S1 Fig in the Supporting Information). The graph was produced by using the i-graph package[13] in R.

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for investigating the effect of weather and/or climate change on water-associated diseases. Conversely, the table contains additional entries that did not emerge from the patterns from Fig 5, but we recognized that they are important for such use (e.g. “Investigation of seasonality” and separation of “Time Series Regression” in short and long term studies).

**Process-based methods (PBM).** Most PBM are based on compartmental models, i.e. a subdivision of the entire population into relevant epidemiological categories, such as susceptible, infected, and recovered people [14]. The population dynamics of each category is usually governed by a system of non-linear differential equations (with each single equation corresponding
### Table 3. Discussion of some key features of the general methods and their relevance to the investigation of the effect of weather and/or climate change.

| PBM | Key aspects of the cluster potentially relevant to study the impact of weather/ climate change | Discussion | Use/Potential use of the method to investigate the effect of weather and/or climate change |
|-----|------------------------------------------------------------------------------------------------|------------|--------------------------------------------------------------------------------------|
| Compartmental models, Spatially explicit compartmental Models (SIR, SIR, SIB, SIB, etc.) | Compartmental models are based on a partition of the entire population into key epidemiological categories, for example, Susceptible, Exposed, Infected, Recovered individuals [13]. When the models are applied to water-borne diseases, often include an additional compartment describing the dynamic of the pathogen population in the environment. This category is usually indicated by W (water) or B (bacteria). Infections occur when a susceptible individual comes in contact with this additional category of the infected category (for human-to-human transmission). Infected people can excrete pathogens, and feed back into the environment compartment. The acronyms (SIR, SEIR, SIB etc.) reflect the specific epidemiological compartments considered. These models typically uses differential equations to estimate the number of individuals in each compartment at any time, but other techniques such as Agent Based Models or difference equations could be employed. | These models are fully specified by a set of parameters (e.g. transmission, recovery, mortality rates etc.) that regulate the transition from one compartment to another. Many of these parameters depend on environmental variables such as temperature. When the functional form of the parameter vs. the environmental variable is known, investigation of the effect of weather and/or climate change on the epidemics is straightforward. | |
| Models Comprising Exposure-Response Relationship | The keywords describing approaches for exposure–response relationship (“Beta-Poisson models”, “Dose-Response models”, “Exposure Model”) also belong to the cluster PBM. In fact many papers that employ exposure–response relationship are integrated with compartmental models as a separate module governing the pathogen dynamics in the environment compartment. | In the present context, exposure–response relationships relate the magnitude of a stressor (e.g. concentration of a pathogen in the water reservoir) to the response of the receptor (e.g. probability of getting infected). The effect of weather/climate on the exposure–response curve can be direct (e.g. an increase in water load due to rainfall results in a diluted concentration affecting the response) or indirect (e.g. when the functional form of the exposure-response curve depends on weather/ climatic variables). | |
| Stability Analysis | All papers employing stability analysis (identified by keywords “Global Stability”, “Local Stability”, “Bifurcation”) are connected within the cluster PBM. This is not surprising as standard OMs are based on sets of differential equations, which is the appropriate environment for stability analysis [89]. | Stability analysis studies if all sufficiently small disturbances away from the equilibrium solution (e.g. a fixed or periodic population), damp out in time [88]. This property depends on the parameter of the system and a variation of a parameter of the system can lead to a transition from stability to instability (bifurcation). In the present context, a change in the environmental parameters (e.g. mean temperature, rainfall) might lead to a transition from disease free equilibrium to an endemic situation or to a variation in the periodicity. | |
| Compartmental Model Calculating Basic Reproductive Number | All papers calculating the reproductive numbers (“Basic Reproductive Number”, “Effective Reproductive Number”, etc.) use PBM approaches. This is usually done analytically from the set of differential equations or by using the Next Generation Matrix approach [87]. | The reproductive number, i.e. the number of secondary cases arising from a primary case under certain conditions, depends on the set of parameters. The approach can be used to investigate which range of the relevant environmental parameters might result in the reproductive number below or above one (i.e. the disease fades out or it establishes). | |
| Human Mobility | Human mobility is often neglected in epidemiological models, however, a small proportion of PBM-papers incorporate human mobility, for example, in the form of “gravity model” [88]. All the reviewed papers, however, focus only on short-term human mobility. | Human mobility will be likely affected by changes in the environmental and socioeconomic factors arising from climate change [89], with an impact on formation and severity of the spatio-temporal epidemic patterns. | |
| Hydrodynamics Model and Network Analysis | The detailed water flow of rivers, estuaries, pipe network etc. can be incorporated in PBM to assess spatio-temporal exposure to contaminated water. This is usually done by employing hydrological models or abstract network theory (see e.g. [115]) where the nodes of the graph represent communities and links represent their connection (hydrological but also due to human mobility). | Hydrodynamics models can take into account variations, due to e.g. rainfall, in the spatio-temporal exposure to the pathogen caused by variations in the contact with contaminated water or in the concentration of the pathogen dispersed in the water. | |
| Compartmental Model with person-to-person Transmission and also person-to-environment transmission | Person-to-person is an additional mode of transmission of many water-associated diseases, e.g. cholera. Many PBM address these processes by allowing infection transmission when a contact between a susceptible and infected person occur. Furthermore, the infected population can excrete pathogens back to the environment, for example via the sewage system. The process can be reproduced by letting the rate of growth of the pathogen population in the environment increases with the number of infected people. | The effects of climate and weather can have an indirect impact on these additional modes of transmission, for example by changing the population size (e.g. due to increased urbanization) and the rates of contact among people, and by altering the patterns of contact at people-environment interface (for instance, socioeconomic factors impacting sewage treatment). | |
| Simulation/Agent Based Models | Only a few studies employed Agent Based Models. These are general methods mimicking the biophysical processes with a computationally-aided set of autonomous, interacting agents. A key advantage is their ability to resolve heterogeneity in a population (which is not necessarily grouped into compartments). | Apart the potentially high computational costs, Agent Based Models are extremely flexible to incorporate specific effects of climate and weather for a variety of situations (e.g. changes in human behavior). These are particularly useful when the mathematical approach is less tractable. | (Continued)
### Table 3. (Continued)

| TS/SE | Key aspects of the cluster potentially relevant to study the impact of weather/climate change | Discussion | Use/Potential use of the method to investigate the effect of weather and/or climate change |
|-------|------------------------------------------------------------------------------------------------|------------|--------------------------------------------------------------------------------------|
| Investigation of seasonality | These studies seek to describe patterns of disease by season. Cosinor and spectral analyses may be used, but also simple tabulation of rates by season. However, in this review we did not find this particular type of studies. | Can give strong indirect information on dependence of disease on weather, but may be misleading if any other risk factors also vary seasonally (e.g. holidays). |  |
| Time Series Regression with Auto-Regressive Models (Disease forecasting studies) | These studies, often using Box-Jenkins methods such as (S)ARIMA, and sometimes incorporating preceding weather as predictors, seek a method to obtain a forecast of disease in the short term future given the series up to the present. | Those forecasting studies that explicitly incorporate weather variables can indirectly provide information on weather-disease associations, but may not separate components that are causal from those due to co-varying factors (e.g. holidays). |  |
| Time series regression I (studies of short term associations) | These studies seek to directly explore the dependence of disease patterns over time on preceding and concurrent weather. Their methods are based on standard GLMs (or occasionally GAMs), in particular Poisson and negative binomial models [15,91]. Most studies control bias from temporal trends and seasonal patterns not necessarily due to weather, and other measured time-varying risk factors. Some allow for residual autocorrelation either using (S)ARIMA or ad hoc approaches (see Time Series Regression with Auto-Regressive Models). | Dependence of disease on weather in the explicit focus of these studies. However, it is unclear how much they could be relied on to predict impact of climate change. One relevant limitation is that they largely ignore the complexity of the dependence as explored in the PBMs. For example very few allow for the variation in susceptible persons due to people becoming immune after contracting the disease. |  |
| Time series regression II (studies of longer term associations) | Studies have explored in particular the association of medium-term weather cycles such as ENSO with disease. Methods options are as for other TSRs, though specifics not. | These have some advantages over TSR of short term associations in being closer to studying association of climate change on health, although they are subject to similar potential biases and their time scales are below the many-decade scale of anthropogenic climate change. |  |
| Spatial Analysis (Cluster Analysis, Geographic information systems (GIS)) | Most spatial methods cover three main areas: Descriptive or visual presentation of data (choropleth maps, GIS), tests for global or local clustering (Moran’s I, spatial scan statistics) and analysing point data to estimate the intensity of spatial processes (kriging, splines) [92–94]. | GIS allows disease data to be linked to datasets (for example, meteorological data) on the basis of geographical location and time. These methods allow the examination of disease risk in relation to space, time and space-time and also allow the interpolation of data points from limited sampling data. |  |
| Spatial Time Series Regression | Spatial time series regression (also called spatio-temporal regression) explores the dependence of infectious disease outcomes with weather when both are measured in units varying over both space and time. | Spatial time series regression maximises contrasts in exposure (variance) when data with both space and time are available. Its main challenges are to control for both spatially and temporally varying confounding variables and autocorrelation. |  |
| Other | Hybrid time series-PBM studies. A few studies employed Hybrid time series-PBM studies. These are applications of ‘time series susceptible-infectious-recovered (immune)’ (TSIR) PBMs incorporating dependence of force of infection on weather [24] overlap with TSR models [15]. | We believe that these approaches have promise to inform dependence of disease on climate and climate change. |  |
| | Bayesian Approach/Markov Chain Monte Carlo | An introduction on Markov Chain Monte Carlo (MCMC) methods, usually associated with Bayesian analysis, is presented in [95,96]. These methods are becoming increasingly popular as they allow estimations of parameters and associated uncertainties for large classes of complex models for which standard estimation is difficult if not impossible. Availability of open source software e.g. WinBugs [87] has largely promoted their use. | These methods are particularly suitable in the presence of complex mechanistic or statistical approaches with many unknown parameters (mirroring the complex impact of weather and/or climate change on water-associated diseases). An important limitation is the computational power required for some models. |  |

[https://doi.org/10.1371/journal.pntd.0005659.t003](https://doi.org/10.1371/journal.pntd.0005659.t003)
to the rate of change of each compartment). This class of models has been extended to stochastic, spatial and age-specific models. The compartmental models in our Review included an additional compartment describing the dynamic of the pathogen population in the environment (e.g. the concentration of the pathogen in the water reservoir) which is then linked in some way to temperature and/or rainfall factors (e.g., rainfall affects the volume of the water reservoir, which determines the dilution of the pathogen and, thus, the probability of contracting the disease; temperature affects the growth and survival of many free living pathogens, such as *E. coli*, in the water reservoir). An infection occurs when a susceptible person comes in contact with this additional category. Infected people can excrete pathogens, and feedback into the environment compartment (included in the majority of the PBM-papers), although for some infections there is no excretion and thus no feedback into the environment (e.g. *Legionella*). Ten percent of PBM-papers also included person-to-person transmission via contacts between susceptible and infected persons. The cluster PBM also contained sub-clusters: “Exposure–Response Relationship”, ”Stability Analysis”, ”Human Mobility”, and ”Network Analysis” (Fig 5). Important features of the clusters are discussed in Table 3.

**Cluster TS-SE.** Time series regression (TSR) analysis [15,17] is one of the most common methods used by the papers reviewed to analyse temperature and rainfall exposures as they can vary over time. Many studies used generalized linear models (GLMs) and generalized additive models (GAMs) often included terms allowing for over-dispersion. Terms to control for seasonality (time stratified model, Fourier terms, spline functions) and autocorrelation terms are often included. In most cases, residual variation in the response variable (e.g. daily counts of disease occurrence) was modelled as a Poisson distribution, followed by negative binomial. The most common exposure factors were temperature and rainfall. Socio-economic indicators were often included in the analysis.

As noted in the systematic review of Imai and Hashizume [15], only a few studies included variations in the susceptible population over time, due to, for instance, changes in immunity following disease recovery. Autoregressive models (e.g. ARMA, ARIMA, SARIMA, ARIMAX), which intrinsically take into account correlation, were used in some studies (Fig 6), although many studies in the regression tradition used ad hoc approaches for this. These methods were often used to investigate the temporal lag between the exposure and the response variable (e.g. daily counts of disease occurrence).

Spatial methods for linking datasets use geographical information systems (GIS) to link disease data with information on socio-economic indicators, temperature and rainfall (or proxy indicators), and vegetation and land use data within the same geographical framework. Georeferenced environmental data can be collected by remote sensing [16,18] and ground-station data.

Other less commonly used analytical methods included wavelet analysis [19], and the social science approach of participatory modelling [20].

**3) Is the method applied to investigate the effects of climate or weather?** Most of the reviewed papers (49% of the papers explicitly emphasized this application in the Abstract) investigated the effects of weather (i.e. short-term changes in the atmosphere, such as daily or weekly exposures to rainfall) on infectious disease. Only 9% of the reviewed papers applied the methodology to study the effects of climate, i.e. long-term averages of weather such as El Niño cycles (these applications are not mutually exclusive); and 7% used modelled future climate projections. Collinearity of exposures, i.e. highly correlated predictor variables in regression models, is an important limitation in weather and climate studies but was only explicitly identified as a limitation in 7% of studies.

**4) Does the type of method depend on the disease/pathogen under investigation?** Approximately 50% of papers investigating *Vibrio cholerae* employed methods based on
compartmental models, followed by time-series/regression analysis and spatial/GIS analysis using cholera case observations. Similar patterns were observed for unspecified water-associated pathogens. As expected, for generic diarrheal pathogens (for which there is much more uncertainty about the causes), spatial/GIS and time-series/regression analysis were the most commonly used methods (but see discussion in [1] and [21]).

5) Some key feature in the methods: e.g. What are the independent variables in the models? Does the model take into account seasonality? More than 70% of studies included observed or modelled temperature and/or rainfall/precipitation data in their analysis. A smaller proportion of studies included (the inclusion is not mutually exclusive) other environmental factors (e.g., relative humidity, vapor air pressure, evaporation) and socio-economic indicators (e.g. access to water, index of poverty, age, education, human mobility) in the analysis (Fig 7).

Around 40% of the methods explicitly included the effects of seasonality (intra-annual climate variability). A small proportion of papers (7%) included the effects of El Niño/Southern Oscillation (ENSO) and North Atlantic Oscillations (NAO). Almost 40% of the methods took into account spatial variation. Only a small proportion of the methods explicitly modelled the pathogen dynamics in the wider environment or the specific water reservoir; a proportion of these studies (typically, theoretical works for a proof of concept) developed general methods without focusing on specific environmental variables, but the method could be potentially applied to investigate their effects.

6) How were the results assessed? The statistical methods used to fit a model with the observed data were assessed with information criteria (such as Akaike Information Criterion, AIC and Bayesian Information Criterion, BIC) in almost 20% of cases. In a significant proportion of papers (10%), the validation of the method was based on out-of-sample predictions, i.e., a subset of the data were used to train/calibrate the method (e.g. to estimate model parameters), and then the method was applied to the rest of the data. In some cases, there was no assessment of the methods. Situations where the methods did not require comparison with real data (e.g. theoretical works requiring solely logical demonstration of theorems) were also present.

7) What are the method limitations for analysing climate and weather effects identified by the authors? The lack of inclusion of relevant factors in the methods was the most common limitation acknowledged by the authors. These included: spatial and socio-economic heterogeneity, seasonality, changing immunity, and other environmental drivers. In almost 20% of papers, the authors identified reporting bias as a key limitation. Examples of reporting bias were: sample collections not properly designed (e.g. not stratified by age); voluntary internet-based survey reflecting survey respondents’ idiosyncrasies; and health-seeking behaviours and socio-economic factors affecting access to health facilities.

The poor quality of the data was another important source of limitation according to the authors, and this was explicitly mentioned in around 30% of reviewed papers. Typical examples of poor data quality were: low spatio-temporal resolution of the exposure data (e.g. environmental exposure covered a wide geographic area or linked to a single weather stations); lack of longitudinal data (only cross-sectional surveys were undertaken); and low accuracy of the data (e.g. reliance on proxy data, missing data due to asymptomatic or unobserved infections).

In 10% of cases, the methods were not able to explain the observed patterns in the disease outcome. The authors identified the absence of underlying mechanistic explanation as a problem in about 10% of the studies. In 10% of papers, the authors highlighted that the methods were calibrated only for a specific situation (e.g. a limited region), and the findings were not generalizable.
Synthesis: Seven challenges in developing methods for quantifying the effects of weather and climate on water-associated diseases

1) Disentangling multiple transmission pathways and identifying the bio-physical mechanism of how weather affects disease and seasonality. In general, the spread of many pathogens is subjected to concurrent modes of transmissions, as exemplified in Fig 1. For instance, cholera can be acquired from contamination of household water storage containers, food preparation, direct person-to-person contacts, and/or via contact with environmental reservoir with long pathogen persistence [22,23]. Identifying a potential signature for the particular pathways in the patterns of diseases is perhaps the ideal goal. In particular, to separate person-to-person transmission from other modes of disease transmissions a range of methods have been proposed, including nonlinear time series approaches linked with wavelet analysis [24] and mechanistic compartmental approaches [22,23]. Despite such efforts, isolating the contributions of person-to-person transmission on the burden of these diseases is a compelling problem not only for water-associated diseases but all infectious diseases [25,26].

Different transmission pathways can be strongly affected by weather and/or climate. For example, temperature may have direct effects on Salmonella bacterial proliferation at various stages in the food chain (including bacterial loads on raw food production, transport and inappropriate storage), and indirect effects on eating behaviours during hot days [27]. Rainfall might increase person-to-environment transmission of cholera, by facilitating the contamination of fresh water from the sewage system. Rainfall might also dilute the concentrations of the pathogens, reducing environment-to-person transmission [28]. Compartmental models have also been used to investigate the effects of pathogen dilution due to the seasonal variation of water volume (e.g. with monsoons) and the potential interactions with other environmental drivers (e.g. temperature [29,30] and the effects of human mobility) [31].

The key challenge ahead are increasing the awareness of the drivers of disease and a deeper integration with fields such as microbiology (e.g. identifying dose-response curves to use as input for modelling, potential coexistence of human-to-human transmission), social science (e.g. to identify and include in the methods social contacts, patterns of mobility, adaptation, etc.), and ecology (e.g. to understand and incorporate the dynamics of free living organisms in water).

2) Reducing uncertainty in reporting. Measuring the ‘true’ incidence of disease, and therefore morbidity and mortality rates, is a common problem in epidemiology. This includes: the under-ascertainment arising when not all cases seek healthcare; under-reporting due to failure in the surveillance system; and reporting bias [32,33]. Community-based studies have been employed to reduce the uncertainty in reporting a range of diseases, including water-associated diseases [34]. These methods usually involve the acquisition of data, e.g. by questionnaire possibly accompanied by biological sampling (e.g. serological surveys), in a representative population such as a retrospective cohorts or a population cross-sections. These methods can be integrated with statistical and mathematical approaches to estimate incidence. For a review of these methods, see [34] and references therein.

A common problem with these methods is that they are sensitive to the particular situation under investigation, such as country, age and social group. In addition, the climate and/or weather can have a direct impact on reporting. For example, impassable roads reducing the ability to seek medical care, and therefore detection, during the rainy season might explain the apparent seasonality of incidence of Lassa fever in humans in Sierra Leone [35]. This last example underscores the importance of integrating a variety of approaches including not only serology, lab-based sampling and statistical/mathematical models, but also participatory modelling and ethnographic research [36] to assess perceptions of risk, approaches to hygiene,
health-seeking behaviour and accessibility; and how economic and social factors affect the reliability of data collection by, or reporting to, the surveillance system [35–37].

3) Identifying the key risk factors/disease determinants and tackling collinearity. A key task is often to detect the main risk factors or disease determinants, and quantify their impacts. A closely related problem is collinearity (also called multi-collinearity), i.e. the situation where two or more predictor variables in a statistical model are linearly related. Collinearity might generate numerical problems, i.e. instability of parameter estimates and inflated variance of the estimated regression coefficient. In particular, collinearity often makes it impossible to attribute the effects on the response variable to the individual predictor variables [38]. This is part of the wider epistemological problem of association vs. causation, which is not discussed here and we refer the interested reader to, for instance, the Bradford-Hill guidelines [39].

In our context, a common source of collinearity is the highly correlated climatic variables such as temperature and rainfall. In some cases, collinearity can have a limited impact on inference, if the correlation between variables remains unchanged [40]. Patterns of collinearity between climatic variables, however, strongly depend on geographic location and environment (e.g. eco-zones) [38]; and they might vary in time due to climate change. This prevents meaningful interpretation/extrapolation of the findings beyond the geographic or environmental range of sampled data.

We share the view of Dormann et al. [38] that without a mechanistic understanding of the biophysical process, collinear variables cannot be separated by statistical means alone. This requires an understanding of the relationships between the different predictor variables, e.g. the dependence of humidity on temperature and rainfall, e.g. [41], or between the response variable and one or more predictor variables, e.g. the dependence of Salmonella growth on temperature.

Such mechanistic insights are not always available and one must rely on solely statistical approaches. Under this scenario, Dormann et al. [38] conducted a systematic review of methods to deal with collinearity and a simulation study evaluating their performance (in absence of mechanistic understanding) with regard to robust model fitting and prediction.

The methodologies assessed in [38], for detecting and removing collinearities include clustering (e.g. Principal Component Analysis-based Clustering, Iterative Variance Inflation Factor Analysis), cluster-independent methods (e.g. Selection of Uncorrelated Variables, Sequential Regression), latent variable regressions (e.g. Principal Component Regression, Partial Least Squares, Dimension Reduction Techniques), and a range of approaches that may be less sensitive to collinearity (e.g. Penalised Regressions, Machine-Learning methods, Collinearity-Weighted Regression). Fourier analysis is another approach that, from each time series of predictor variables, extracts a set of orthogonal data to be used as new descriptor uncorrelated variables [18,42]. Bayesian Network Analysis is another promising tool to identify statistical dependencies between multiple variables, and to separate these into those directly and indirectly dependent with one or more response variables [43]. This data-driven statistical tool produces a graphical network, whose structure describes the interdependency between variables [43,44]. In contrast with Path Analysis [45], Bayesian network analysis does not assume any causal relationships although this can be introduced by appropriate prior distribution for the structure of the graphical network. In particular, the method has been applied to investigate socioeconomic determinants for diarrheal diseases and the role of weather in animal diseases [43,46]. Another method, applied to the 1993 Milwaukee Cryptosporidium outbreak [47], integrates population dynamic models with Profile Likelihood approach [48]. The problem of collinearity is removed by fixing the value of one or more parameters, and then estimating the remaining ones by maximizing the (log-) likelihood of the associated model; the approach is
then repeated for a range of values of the fixed parameters. The method, which is suitable for a limited subset of the parameters, provides a better understanding of the relationship among different parameters.

4) Identifying and quantifying the different sources of the temporal lag from the start of the pathway to infection to disease detection. The effects of the different meteorological, climatic, environmental and socio-economic factors on occurrence of disease are not instantaneous. Fig 1 illustrates some of the complexity. Sources of the temporal lag include the time required for potential growth of pathogen population in the environment, exposure dynamics, incubation period, and delays in reporting.

Further complications can arise from feedback from the infected population to the pathogen reservoir (e.g. rainfall facilitating contamination of fresh water from the sewage system). The required time $t_{res}$, for the pathogen population in the reservoir to replicate and reach a sufficient value to cause infections, depends on a range of environmental and microbiological factors specific to the pathogen under investigation. Methods to estimate this time and its distribution are beyond the scope of this Review; here we simple mention some mechanistic approaches and a separate published review for temperature-driven bacterial growth in food and in water drinking systems [49–53]. The required time $t_{exp}$ for susceptible individuals to be infected after being exposed to the pathogen reservoir, depends on the particular route of transmission and type of exposure.

The literature on microbial risk assessment framework (hazard identification, dose-response relationships, exposure assessment, quantitative risk characterization) represents an important source of methods to estimate the probability of infection and disease resulting from exposure to a variety of pathogenic microorganisms [54–56]. The effect of exposure events is, in general, distributed over a time interval. A range of approaches, based on time series analysis, has been implemented to study the distributed effects of multiple episodes of exposure on infectious outbreaks (see [57] and references therein). A general statistical framework that can simultaneously represent non-linear exposure–response dependencies (due to, for example, depletion of susceptibles) and delayed effects has been recently formulated [58].

Infections are typically revealed after the incubation period, $t_{inc}$ (the time between infections and symptoms onset); which is associated with patient’s physiology, whose distribution depends on the type of infection (see historical paper of Sartwell [59]). After symptoms start, only a proportion of the infected individuals seeks medical assistance (see issue above on reporting), and for only a proportion of these cases further diagnostic testing will be conducted and recorded in the public health system. This introduces a further time lag, $t_{det}$, between the time when infected individual approaches the health system and the actual appropriate laboratory detection with diagnosis [60,61]. Even in a simple scenario, the temporal lag between the start of the pathway to infection (which can be challenging to define) and disease detection is a combination the time lags $t_{res}$, $t_{exp}$, $t_{inc}$, $t_{det}$. These are typically represented by random variables drawn from adequate distributions; for example a log-normal distribution has been proposed for $t_{inc}$ and $t_{det}$.

Key challenges include: these distributions are expected to be dependent on a range of factors (patient’s physiology, environment, reporting bias), they are not necessarily stationary [61], and the technical difficulties inherent with the algebra of random variables [62]. Estimating the time lag between environmental/climatic variables and infections was a common task encountered in this Review, however, none of the methods used distinguished the different sources of time lag, and in most cases the assessment was based on trial and error methods (typically, searching for high correlation between the time series of incidence and the time series of temperature and/or rainfall at 1,2, etc. weeks before the date of reported case) followed by some significance tests or selection criteria (e.g. p-values, AIC [63]).
Involving the wider community via community-based studies and citizen science could help in identifying the different sources of the temporal lag from the start of the pathway to infection to disease detection. This information could be used as inputs for agent based models (ABM) to simulate controlled processes in epidemics, and to assess the capability of these models to identify the multiple sources (physiology, environment, behaviour) of time lags and their statistical distributions.

5) **Studying the evolution of pathogen in response to climate change/variability.** Very little research has investigated the potential effect of observed climate change/variability on

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Fig 7. The most common environmental and socio-economic variables included in the reviewed papers.

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the evolution and adaptation of pathogens [56], that is changes in the climate (e.g. mean temperature and rainfall, patterns of seasonality, etc.) on over decadal time scales. In particular, seasonality is expected to be an important driver of pathogen evolution (see [64–66] and references therein), as periods of high transmission are followed by population bottlenecks reducing strain diversity and causing rapid genetic shifts. Furthermore, external periodic perturbations (e.g. seasonality in temperature, rainfall) can resonate with the natural frequencies of the ecosystem, promoting emergency or suppression of particular strains of the pathogen [66]. Apart from the theoretical work of Koelle et al [67] which might explain the cholera strain replacement in Bangladesh due to changes in monsoon rainfall patterns, we are not aware of further research investigating evolution of water-associated pathogens in response to climate change.

6) Investigating the effects of time-varying factors on transmission patterns. The importance of and challenges in understanding the effects of seasonal drivers and climate variability on the dynamics of infectious diseases are largely recognized [24,64,68–71] and not repeated here. Further challenges arise from potential changes in seasonal patterns of the drivers, for example due to control measures, and aperiodic time-varying factors [72]. Stability analysis for seasonal systems, i.e. studying the conditions for pathogen invasion and establishment in systems characterized by fluctuating environmental forcing (based for example on Floquet analysis [30,73]), represents an interesting area for future research.

7) Dealing with different spatio-temporal scales. The mechanistic approaches reviewed here were in most cases deterministic compartmental models, which are strictly only valid for large epidemics. Water-associated disease outbreaks could be point-source, affecting a relatively small population. For this situation, stochastic process-based models coupled with local weather and environmental variables could be beneficial. Quantitative methodological studies applied to longer term climatic effects are limited. Extreme events, such as prolonged droughts (months or years) and heavy rain events (days or weeks), are expected to have a major impact on the dynamics of infectious diseases [74–77]. The papers reviewed here focused on the intensity of the events alone, not their frequency. Furthermore, there is no consensus on the definition of extreme weather events [77].

None of the reviewed paper investigated the long term effect of human adaptation to climatic change. The effects of Earth atmosphere range from short term weather events, to intermediate time periods events like ENSO, to longer term climate change. We are not aware of any unified approach linking together the effects of the different time-scales on water-associated infectious diseases and their spatial distribution. Spatial analysis was often performed on a temporal snapshot (cross sectional study), usually to find correlation among different variables on different locations. Only a small proportion of spatial studies included temporal dynamics, for example to study the spread of cholera in a particular region due to rainfall. Longer term changes, such as land use changes, were rarely incorporated.

Discussion

A range of diverse methods are used to study the effect of weather and climate on water-associated diseases. Most of these methods can be connected to two main groups: (i) process based models (PBM), and (ii) time series and spatial epidemiology. In general, PBM were employed when the bio-physical mechanism of transmission of the pathogen was known (as with *Vibrio cholerae*, the most studied pathogen). PBMs describe the progression of the infectious diseases by mimicking the bio-physical processes, typically, in terms of non-linear differential equations [14]. In contrast, statistically-oriented approaches (such as regression analysis over space or over time) tended to be used when the roles of specific environmental drivers were unclear.
and the methods needed to find potential correlates between environmental and/or socio-economic variables and patterns of infections.

The two clusters resemble the groups of explanatory and predictive models. Although we recognize the importance of the debate in the philosophy of science about these two groups of models [10], we avoided a formal grouping of the studies according to this classification. Applying the guidelines provided by Shmueli [10] in a rigorous and objective manner was particularly challenging in our contest. For example, many modelling studies (e.g. [78]) provide maps of the risk of a disease, i.e. they make predictions, by calculating the Basic Reproductive Number, which is a typical tool in explanatory compartmental models as built on "First Principles". Should these models be classified as predictive or explanatory?

The use, or potential use, of the reviewed methodologies to investigate the effects of weather and/or climate is discussed in Table 3. Most of the studies focused on the short-term effects of weather as these time series of health data are more readily available.

Teasing apart the individual effects of multiple abiotic factors (e.g. weather, climate, environmental, demographic, and socio-economic) on the incidence of water-associated infectious diseases is the main challenge. Additional challenges include many other methodological problems arising from the limited understanding of the complex bio-physical mechanisms, concurrent effects of many correlated factors, poor data quality and reporting bias, and uncertainty in the knowledge of relevant parameters; these are all intrinsic limitations of the methods and the data available. Addressing these challenges would enable the formulation of a framework to understand the overall effects of weather, climate, and possibly other environmental and socio-economic factors on water-associated infectious disease.

This research has the common limitations of any systematic review. An important one is the possibility we have missed relevant studies, for example due to the failure of the search engine or studies written in languages other than English. This problem could be overcome, at least in part, by the application of snowballing procedures, i.e. recursively pursuing relevant references cited in the retrieved literature and then adding them to the search results [79]. This technique is less feasible when the initial pool of documents is as large as in the current case.

Nevertheless, considering the high number of studies included in this Review, we expect that the general patterns in our findings are robust. We recognize that there are methods developed and applied to other different classes of infectious diseases (e.g. vector-borne diseases) potentially relevant to our context which were not included in our analysis. The protocol of our review was chosen to ensure the objectivity and reproducibility of the results and the research question we identified.

Recommendations for future research

The choice of a particular method in a study is driven by many factors, including the scientific background of the scientists involved (anecdotally, we noticed that most PBM are employed by scientists working in engineering or physics departments); the ease in implementing the methods (e.g. using freely available statistical packages); and probably the tendency to use already widely used methods, a phenomenon known as the Matthew Effect [80,81]. The choice of the methods ought to be driven by many factors, i.e. the scientific questions, the availability of data, the transmission pathways, and the bio-physical and socio-economic mechanism, as well as the state of the art of the methods. These should be critically assessed on a case-by-case basis, and not based on oversimplified, prescriptive guidelines. The findings of this Review can assist scientists in the critical selection and development of methods for quantifying the effects of weather and climate on water-associated diseases.
**Tackling the many challenges.** Important data and theoretical challenges emerged with implications for the surveillance and control of water-associated infections. The inter-connections between human health, the environment, and also animal health as advocated by the One Health holistic vision [82], are increasingly recognized. Being aware of these connections and the potential bio-physical mechanisms occurring at different spatio-temporal scales is crucial to separate out the multiple transmission pathways, to understand and quantify the different sources of the temporal lag, and to deal with collinearity. Incorporating information on human behaviour and socio-economic factors can help to reduce reporting bias, and improve understanding of the potential effect on infectious diseases of anthropogenic climate change and interventions.

**Collecting and linking long term, high-resolution, epidemiological, socio-economic, environmental and climatic data.** The integration of infection data with long-term, national-scale, environmental and land use data is an important growing approach [83]. For example, the national communicable diseases database of Public Health England has collected data from microbiology diagnostic laboratories (as well as patient’s addresses in the last five years) for England and Wales since 1989. The location of the diagnostic laboratories, or the patient residences, could be used to link cases to local weather parameters supplied by the UK Met Office in a confidential manner. These cases could also be linked with the spatial density of livestock data. The utility of these datasets could be further improved, as most current datasets are one-off surveys. Data on the spatio-temporal infection prevalence in livestock are also important information.

The paucity of this kind of information is much more pronounced for data on wildlife; with the exception of voluntary based schemes (such as citizen science [84]), we are not aware of a systematic collection of such data. Involving the wider public via community-based studies and citizen science could help in reducing the uncertainty in reporting and in identifying the different sources of the temporal lag from the start of the pathway to infection to disease detection. For example, surveys could be used by public health institutions to gather data on patient behaviour, symptom onset, food and water exposures, the likelihood of seeking medical advice, and the location of the potential sources of infection, etc.

**Integrating bio-physical and socio-economic mechanisms of infectious disease.** The emergence, risk, spread, and control of infectious diseases are affected by many complex bio-physical, environmental and socio-economic factors [1]. These include climate and environmental change, land-use variation, and changes in population and human behaviour. For example, the abundance of long term, high-resolution, surveillance data (e.g. reported infectious diseases from Public Health England) linked with local weather parameters allows the analysis of the subset of epidemiological cases when all environmental variables (except one predictor, referred to as 'test variable') are fixed; in this way, the problem of collinearity is naturally removed. This exercise provides a family of curves of the rates of infection, which are function of the test variable and conditioned to all other fixed predictors. From the family of curves, the potential relationship between the predictors and the rate of infection can be inferred and potentially elucidate the bio-physical mechanism.

Conversely, functional relationships between epidemiological measures (e.g. incidence) and weather parameters arising from process-based models could be used as inputs for statistical models (e.g. by providing a particular relationship for the link function in a GLM). Feedbacks from community-based studies on human behaviour could also be integrated with process-based and statistical methods to design more realistic mathematical models, which in turn can assist with making policy decisions [35].
Supporting information

S1 Text. Technical keywords/expressions used in the documents.
(DOCX)

S2 Text. List of search words used for the MEDLINE database.
(DOC)

S1 Table. List of included papers.
(XLSX)

S1 Fig. High resolution, zoomable image for Fig 5.
(TIFF)

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References

1. Mellor JE, Levy K, Zimmerman J, Elliott M, Bartram J, Carlton E, et al. Planning for climate change: The need for mechanistic systems-based approaches to study climate change impacts on diarrhoeal diseases. Sci Total Environ. Elsevier B.V.; 2016; 548–549: 82–90. https://doi.org/10.1016/j.scitotenv.2015.12.087 PMID: 26799810

2. World Health Organization. Neglected Tropical Diseases [Internet]. 2017 [cited 3 Apr 2017]. http://www.who.int/neglected_diseases/diseases/en/

3. CDC. Which diseases are considered Neglected Tropical Diseases? [Internet]. [cited 3 Apr 2017]. https://www.cdc.gov/globalhealth/ntd/diseases/index.html

4. PLOS Neglected Tropical Diseases. Journal Information [Internet]. [cited 3 Apr 2017]. http://journals.plos.org/plosntds/s/journal-information
5. Bain R, Cronk R, Hossain R, Bonjour S, Onda K, Wright J, et al. Global assessment of exposure to faecal contamination through drinking water based on a systematic review. Trop Med Int Heal. 2014; 19: 917–927. https://doi.org/10.1111/tmi.12334 PMID: 24811893

6. WHO. Preventing diarrhoea through better water, sanitation and hygiene: exposures and impacts in low- and middle-income countries [Internet]. 2014. http://apps.who.int/iris/bitstream/10665/150112/1/9789241564823_eng.pdf?ua=1

7. Prüss-Ustün A, Bartram J, Clasen T, Colford JM, Cumming O, Curtis V, et al. Burden of disease from inadequate water, sanitation and hygiene in low- and middle-income settings: a retrospective analysis of data from 145 countries. Trop Med Int Heal. 2014; 19: 894–905. https://doi.org/10.1111/tmi.12329 PMID: 24779548

8. Campbell OMR, Benova L, Gon G, Afshana K, Cumming O. Getting the basic rights—the role of water, sanitation and hygiene in maternal and reproductive health: A conceptual framework. Trop Med Int Heal. 2015; 20: 252–267. Available: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=emed12&AN=2015644699

9. Goldberg RJ, McManus DD, Allison J. Greater knowledge and appreciation of commonly-used research study designs. Am J Med. 2013; 126: 1–16.

10. Shmueli G. To explain or to predict? Stat Sci. 2010; 25: 289–310. https://doi.org/10.1214/10-STS330

11. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JPA, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. PLoS Med. 2009; 6: e1000100. https://doi.org/10.1371/journal.pmed.1000100 PMID: 19621070

12. R Development Core Team. R: A Language and Environment for Statistical Computing [Internet]. Vienna, Austria: R Foundation for Statistical Computing; 2008. http://www.r-project.org

13. Csardi G, Nepusz T. The igraph software package for complex network research. InterJournal, Complex Syst. 2006; 1695. Available: papers2:/publication/uuid/81D474A3-7138-4323-9DB1-846B5EB27B1F

14. Anderson RM, May RM. Infectious diseases of humans: dynamics and control. Oxford University Press; 1991.

15. Imai C, Hashizume M. A Systematic Review of Methodology: Time Series Regression Analysis for Environmental Factors and Infectious Diseases. Trop Med Health. 2015; 43: 1–9. https://doi.org/10.2149/tmth.2014-21 PMID: 25859149

16. Rogers DJ, Randolph SE. Studying the global distribution of infectious diseases using GIS and RS. Nat Rev Microbiol. 2003; 1: 231–7. https://doi.org/10.1038/nrmicro776 PMID: 15035027

17. Bhaskaran K, Gasparini A, Hajat S, Smeeth L, Armstrong B. Time series regression studies in environmental epidemiology. Int J Epidemiol. 2013; 42: 1187–1195. https://doi.org/10.1093/ije/dyt092 PMID: 23760528

18. Rogers DJ, Williams BG. Tsetse distribution in Africa: seeing the wood and the trees. In: Edwards PJ, May RM, Webb NR, editors. Large-Scale Ecology and Conservation Biology. Oxford, UK: Blackwell Scientific Publications; 1994. pp. 247–272.

19. Cazelles B, Chavez M, de Magny GC, Guegan JF, Hales S. Time-dependent spectral analysis of epidemiological time-series with wavelets. J R Soc Interface. 2007; 4: 625–636. https://doi.org/10.1098/rsif.2007.0212 PMID: 17301013

20. Cornwall A, Jewkes R. What is participatory research? Soc Sci Med. 1995; 41: 1667–1676. https://doi.org/10.1016/0277-9536(95)00127-S PMID: 8746866

21. Levy K, Woster AP, Goldstein RS, Carlton EJ. Untangling the Impact of Climate Change on Waterborne Diseases: A Systematic Review of Relationships between Diarrheal Diseases and Temperature, Rainfall, Flooding, and Drought. Environ Sci Technol. 2016; 50: 4905–4922. https://doi.org/10.1021/acs.est.5b06186 PMID: 27058059

22. Tien JH, Eam DJD. Multiple transmission pathways and disease dynamics in a waterborne pathogen model. Bull Math Biol. 2010; 72: 1506–1533. Available: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=emed10&AN=20143271 https://doi.org/10.1007/s11538-010-9507-6 PMID: 20143271

23. Robertson SL, Eisenberg MC, Tien JH. Heterogeneity in multiple transmission pathways: modelling the spread of cholera and other waterborne disease in networks with a common water source. J Biol Dyn. 2013; 7: 254–275. https://doi.org/10.1080/17513758.2013.853844 PMID: 24303905

24. Koelle K, Pascual M. Disentangling extrinsic from intrinsic factors in disease dynamics: a nonlinear time series approach with an application to cholera. Am Nat. 2004; 163: 901–13. https://doi.org/10.1086/420798 PMID: 15266387

25. Lo Iacono G, Cunningham AA, Fichet-Calvet E, Garry RF, Grant DS, Khan SH, et al. Using Modelling to Disentangle the Relative Contributions of Zoonotic and Anthroponotic Transmission: The Case of
Lassa Fever. McElroy AK, editor. PLoS Negl Trop Dis. Public Library of Science; 2015; 9: e3398. https://doi.org/10.1371/journal.pntd.0003398 PMID: 25569707

26. Lo Iacono G, Cunningham AA, Fichtet-Calvet E, Garry RF, Grant DS, Leach M, et al. A Unified Framework for the Infection Dynamics of Zoonotic Spillover and Spread. Foley J, editor. PLoS Negl Trop Dis. 2016; 10: e004957. https://doi.org/10.1371/journal.pntd.0004957 PMID: 27588425

27. Zhang Y, Bi P, Hiller J. Climate variations and salmonellosis transmission in Adelaide, South Australia: a comparison between regression models. Int J Biometeorol. Berlin; Germany: Springer-Verlag GmbH; 2007; 52: 179–187. Available: http://search.embamount.com/login.aspx?direct=true&db=ihh&AN=2008303642&site=ehost-live

28. Pascual M, Bouma MJ, Dobson AP. Cholera and climate: Revisiting the quantitative evidence. Microbes Infect. 2002; 4: 237–245. https://doi.org/10.1016/S1286-4579(01)01533-7 PMID: 11880057

29. Righetto L, Casagrandi R, Bertuzzo E, Mari L, Gatto M, Rodriguez-Iturbe I, et al. The role of aquatic reservoir fluctuations in long-term cholera patterns. Epidemics. 2012; 4: 33–42. Available: http://ovidsp.ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=emed&AN=22325012 https://doi.org/10.1016/j.epidem.2011.11.002 PMID: 22325012

30. Mari L, Casagrandi R, Bertuzzo E, Rinaldo A, Gatto M. Floquet theory for seasonal environmental forcing of spatially explicit waterborne epidemics. Theor Ecol. 2014; 351–365. https://doi.org/10.1007/s12080-014-0223-y

31. Mari L, Bertuzzo E, Righetto L, Casagrandi R, Gatto M, Rodriguez-Iturbe I, et al. Modelling cholera epidemics: The role of waterways, human mobility and sanitation. J R Soc Interface. 2012; 9: 376–388. Available: http://ovidsp.ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=emed&AN=2012072693 https://doi.org/10.1098/rsif.2011.0304 PMID: 21752809

32. Kopec J a, Esdaile JM. Bias in case-control studies. A review. J Epidemiol Community Heal. 1990; 44: 179–186. https://doi.org/10.1136/jech.44.3.179

33. Gibbons CL, Mangen M-JJ, Plass D, Havelaar AH, Brooke RJ, Kramarz P, et al. Measuring underreporting and under-ascertainment in infectious disease datasets: a comparison of methods. BMC Public Health. 2014; 14: 147. https://doi.org/10.1186/1471-2458-14-147 PMID: 24517715

34. Gibbons CL, Mangen M-JJ, Plass D, Havelaar AH, Brooke RJ, Kramarz P, et al. Measuring underreporting and under-ascertainment in infectious disease datasets: a comparison of methods. BMC Public Health. 2014; 14: 147. https://doi.org/10.1186/1471-2458-14-147 PMID: 24517715

35. Grant C, Lo Iacono G, Dzingirai V, Bett B, Winnebah TRA, Atkinson PM. Moving interdisciplinary science forward: integrating participatory modelling with mathematical modelling of zoonotic disease in Africa. Infect Dis Poverty. BioMed Central; 2016; 5: 17. https://doi.org/10.1186/s40249-016-0110-4 PMID: 26916067

36. Leach M, Scoones I. The social and political lives of zoonotic disease models: narratives, science and policy. Soc Sci Med. Elsevier Ltd; 2013; 88: 10–7. https://doi.org/10.1016/j.socscimed.2013.03.017 PMID: 23702205

37. Scoones I, Jones K, Lo Iacono G, Redding D, Wilkinson A, Wood J. Integrative modelling for One Health: pattern, process and participation. Philos Trans R Soc London B Biol Sci. 2017; 372: 20160164. https://doi.org/10.1098/rstb.2016.0164 PMID: 28584172

38. Dormann CF, Elith J, Bacher S, Buchmann C, Carl G, Carré G, et al. Collinearity: a review of methods to deal with it and a simulation study evaluating their performance. Ecography (Cop). 2013; 36: 027–046. https://doi.org/10.1111/j.1600-0587.2012.07348.x

39. Hill AB. the Environment and Disease: Association or Causation? Proc R Soc Med. 1965; 58: 295–300. Available: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=1898525&tool=pmcentrez&rendertype=abstract PMID: 14283879

40. Regression Modeling Strategies: With Applications to Linear Models, Logistic Regression, and Survival Analysis (Springer Series in Statistics): Amazon.co.uk : Harrell Frank E., Harrell F. E.: 9780387952321: Books [Internet].

41. Eccel E. Estimating air humidity from temperature and precipitation measures for modelling applications. Meteorol Appl. 2012; 19: 118–128. https://doi.org/10.1002/met.258

42. Rogers DJ. Satellites, space, time and the African trypanosomiases. Advances in Parasitology. 2000. pp. 129–171. https://doi.org/10.1016/S0065-308X(00)47008-9 PMID: 10997206

43. Lewis FI, McCormick BJJ. Revealing the Complexity of Health Determinants in Resource-poor Settings. Am J Epidemiol. 2012; 176: 1051–1059. https://doi.org/10.1093/aje/kws183 PMID: 23139247

44. Needham CJ, Bradford JR, Bulpitt AJ, Westhead DR. A primer on learning in Bayesian networks for computational biology. PLoS Comput Biol. 2007; 3: 1409–1416. https://doi.org/10.1371/journal.pcbi.0030129 PMID: 17784779
45. Pedhazur EJ. Multiple Regression in Behavioral Research: explanation and prediction. third. USA: Holt, Rinehart & Winston; 1982.
46. McCormick BJJ, Sanchez-Vazquez MJ, Lewis FL. Using Bayesian networks to explore the role of weather as a potential determinant of disease in pigs. Prev Vet Med. Elsevier B.V.; 2013; 110: 54–63. https://doi.org/10.1016/j.prevetmed.2013.02.001 PMID: 23465608
47. Brookhart MA, Hubbard AE, van der Laan MJ, Colford JM Jr., Eisenberg JN. Statistical estimation of parameters in a disease transmission model: analysis of a Cryptosporidium outbreak. Stat Med. 2002; 21: 3627–3638. Available: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=med4&AN=12436460 https://doi.org/10.1002/sim.1258 PMID: 12436460
48. Cole SR, Chu H, Greenland S. Maximum likelihood, profile likelihood, and penalized likelihood: A primer. Am J Epidemiol. 1990; 56: 1875–1881. PMID: 16348228
49. Baranyi J, Roberts TA. A dynamic approach to predicting bacterial growth in food. Int J Food Microbiol. 1994; 23: 277–294. https://doi.org/10.1016/0168-1605(94)90157-0 PMID: 8783331
50. Janis Rubulis, Talis Juhna, Lars Henning AK. Methodology of Modeling Bacterial Growth in Drinking Water Systems [Internet]. 2007. http://www.techneau.org/
51. Sant'Ana AS, Franco BDGM, Schaffner DW. Modeling the growth rate and lag time of different strains of Salmonella enterica and Listeria monocytogenes in ready-to-eat lettuce. Food Microbiol. Elsevier Ltd; 2012; 30: 267–273. https://doi.org/10.1016/j.fm.2011.11.003 PMID: 22265311
52. Eisendberg JN, Seto EYW, Olivieri AW, Spear RC. Quantifying water pathogen risk in an epidemiological framework. Risk Anal. 1996; 16: 549–563. Available: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=emed4&AN=1996300886 PMID: 8919345
53. Geller L. Under the Weather: Climate, Ecosystems, and Infectious Disease. Emerg Infect Dis. Washington, D.C: National Academy Press; 2001; 7: 606–608. https://doi.org/10.3201/eid0707.017750
54. Haas CN, Rose JB, Gerba CP. Quantitative Microbial Risk Assessment [Internet]. John Wiley & Sons; 1999. https://books.google.com/books?hl=en&lr=&id=vjVhhwQh9N8C&pgis=1
55. Marinovic AB, Swaan C, van Steenbergen J, Kretzschmar M. Quantifying reporting timeliness to improve outbreak control. Emerg Infect Dis. 2015; 21: 209–16. https://doi.org/10.3201/eid2102.130504 PMID: 25625374
56. Altizer S, Dobson A, Hosseini P, Hudson P, Pascual M, Rohani P. Seasonality and the dynamics of infectious diseases. Ecol Lett. 2006; 9: 467–484. Available: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=med5&AN=16623732 https://doi.org/10.1111/j.1461-0248.2005.00879.x PMID: 16623732
57. Donnelly R, Best a, White a, Boots M. Seasonality selects for more acutely virulent parasites when virulence is density dependent. Proc Biol Sci. 2013; 280: 20122464. https://doi.org/10.1098/rspb.2012.2464 PMID: 23193313
58. Lo Iacono G, van den Bosch F, Gilligan CA. Durable Resistance to Crop Pathogens: An Epidemiological Framework to Predict Risk under Uncertainty. van Bruggen A, editor. PLoS Comput Biol. Public Library of Science; 2013; 9: e1002870. https://doi.org/10.1371/journal.pcbi.1002870 PMID: 23341765
59. Koelle K, Pascual M, Yunus M. Pathogen adaptation to seasonal forcing and climate change. Proc R Soc B Biol Sci. 2005; 272: 971–977. Available: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=emed7&AN=2005307535
68. Grassly NC, Fraser C. Seasonal infectious disease epidemiology. Proc Biol Sci. 2006; 273: 2541–50. https://doi.org/10.1098/rspb.2006.3604 PMID: 16959647

69. Fisman DN. Seasonality of infectious diseases. Annu Rev Public Health. 2007; 28: 127–43. https://doi.org/10.1146/annurev.publhealth.28.021406.144128 PMID: 17222079

70. Kovats RS, Bouma MJ, Hajat S, Worrall E, Haines A. El Niño and health. Lancet. 2003; 362: 1481–1489. https://doi.org/10.1016/S0140-6736(03)14695-8 PMID: 14602445

71. Rodó X, Pascual M, Fuchs G, Faruque ASG. ENSO and cholera: a nonstationary link related to climate change? Proc Natl Acad Sci U S A. 2002; 99: 12901–6. https://doi.org/10.1073/pnas.182203999 PMID: 12228724

72. Remais J, Zhong B, Carlton EJ, Spear RC. Model approaches for estimating the influence of time-varying socio-environmental factors on macroparasite transmission in two endemic regions. Epidemics. 2009; 1: 213–220. Available: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGET=fulltext&D=med5&AN=20454601 https://doi.org/10.1016/j.epidem.2009.10.001 PMID: 20454601

73. Klausmeier Ca. Floquet theory: a useful tool for understanding nonequilibrium dynamics. Theor Ecol. 2008; 1: 153–161. https://doi.org/10.1007/s12080-008-0016-2

74. Easterling DR, Mearns LO. Climate extremes: observations, modeling, and impacts. Science. 2000; 289: 2068–2074. https://doi.org/10.1126/science.289.5487.2068 PMID: 11000103

75. Epstein PR. Climate change and emerging infectious diseases. Microbes Infect. 2001; 3: 747–754. https://doi.org/10.1046/s1286-4579(01)01429-0 PMID: 11489243

76. McMichael AJ, Campbell-Lendrum DH, Corvalan CF, Ebi KL, Giltheko AK, Scheraga JD, et al., editors. Climate change and human health: Risks and responses [Internet]. Geneva: World Health Organization; 2003. http://www.who.int/globalchange/environment/en/ccSCREEN.pdf?ua=1

77. Guzman Herrador BR, de Blasio BF, Macdonald E, Nichols G, Sudre B, Vold L, et al. Analytical studies assessing the association between extreme precipitation or temperature and drinking water-related waterborne infections: a review. Environ Heal. 2015; 14: 29. https://doi.org/10.1186/s12940-015-0014-y PMID: 25885050

78. Lo Iacono G, Robin CA, Newton JR, Gubbins S, Wood JLN. Where are the horses? With the sheep or cows? Uncertain host location, vector-feeding preferences and the risk of African horse sickness transmission in Great Britain. J R Soc Interface. 2013; 10: 20130194-. https://doi.org/10.1098/rsif.2013.0194 PMID: 23594817

79. Choong MK, Galgani F, Dunn AG, Tsafnat G. Automatic evidence retrieval for systematic reviews. J Med Internet Res. Journal of Medical Internet Research; 2014; 16: e223. https://doi.org/10.2196/jmir.3369 PMID: 25274020

80. Merton RK. The Matthew Effect in Science: The reward and communication systems of science are considered. Science (80-). American Association for the Advancement of Science; 1968; 159: 56–63. https://doi.org/10.1126/science.159.3810.56 PMID: 17737466

81. Perc M. The Matthew effect in empirical data. J R Soc Interface. 2014; 11: 20140378–20140378. https://doi.org/10.1098/rsif.2014.0378 PMID: 24990288

82. Rabinowitz PM, Kock R, Kachani M, Kunkel R, Thomas J, Gilbert J, et al. Toward Proof of Concept of a One Health Approach to Disease Prediction and Control. Emerg Infect Dis. Centers for Disease Control and Prevention; 2013; 19. https://doi.org/10.3201/eid1912.130265 PMID: 24295136

83. Fleming LE, Haines A, Golding B, Kessel A, Cichowska A, Sabel CE, et al. Data mashups: Potential contribution to decision support on climate change and health. Int J Environ Res Public Health. 2014; 11: 1725–1746. https://doi.org/10.3390/ijerph110201725 PMID: 24499879

84. Riesch H, Potter C. Citizen science as seen by scientists: Methodological, epistemological and ethical dimensions. Public Underst Sci. 2014; 23: 107–120. https://doi.org/10.1177/0963662513497324 PMID: 23982281

85. May RM. Stability and Complexity in Model Ecosystems. 2nd ed. Princeton: Princeton University Press; 2001.

86. Steven S. Nonlinear dynamics and chaos [Internet]. Reading, Massachusetts: Perseus Books; 2001. http://onlinelibrary.wiley.com/doi/10.1038/npg.els.0003314/full

87. Diekmann O, Heesterbeek J a P, Roberts MG. The construction of next-generation matrices for compartmental epidemic models. J R Soc Interface. 2010; 7: 873–85. https://doi.org/10.1098/rsif.2009.0386 PMID: 19892718

88. Erlander S, Stewart NF. The gravity model in transportation analysis: theory and extensions. CRC Press; 1990.

89. Hastrup K, Olwig KF, editors. Climate Change and Human Mobility Challenges to the Social Sciences. Cambridge University Press; 2012.
90. Gatto M, Mari L, Bertuzzo E, Casagrandi R, Righetto L, Rodriguez-Iturbe I, et al. Generalized reproduction numbers and the prediction of patterns in waterborne disease. Proc Natl Acad Sci. 2012; 109: 19703–19708. https://doi.org/10.1073/pnas.1217567109 PMID: 23150538

91. Imai C, Armstrong B, Chalabi Z, Mangtani P, Hashizume M. Time series regression model for infectious disease and weather. Environ Res. Elsevier; 2015; 142: 319–327. https://doi.org/10.1016/j.envres.2015.06.040 PMID: 26188633

92. Osei FB. Current Statistical Methods for Spatial Epidemiology: A Review. Austin Biometrics Biostat. 2014; 1: 7.

93. Ostfeld RS, Glass GE, Keesing F. Spatial epidemiology: An emerging (or re-emerging) discipline. Trends Ecol Evol. 2005; 20: 328–336. https://doi.org/10.1016/j.tree.2005.03.009 PMID: 16701389

94. Diggle PJ. Statistical Analysis of Spatial and Spatio-Temporal Point Patterns [Internet]. Third. Chapman and Hall/CRC; 2013. https://www.crcpress.com/Statistical-Analysis-of-Spatial-and-Spatio-Temporal-Point-Patterns-Third/Diggle/p/book/9781466560239

95. Hamra G, MacLehose R, Richardson D. Markov chain monte carlo: An introduction for epidemiologists. Int J Epidemiol. 2013; 42: 627–634. https://doi.org/10.1093/ije/dyt043 PMID: 23569196

96. Gilks WR (Wally R.), Richardson S (Sylvia), Spiegelhalter DJ. Markov chain Monte Carlo in practice [Internet]. Chapman & Hall; 1996. https://www.crcpress.com/Markov-Chain-Monte-Carlo-in-Practice/Gilks-Richardson-Spiegelhalter/p/book/9780412055515

97. Lunn D, Spiegelhalter D, Thomas A, Best N. The BUGS project: Evolution, critique and future directions. Stat Med. 2009; 28: 3049–3067. https://doi.org/10.1002/sim.3680 PMID: 19630097