A systematic review and meta-analysis of the effects of extreme weather events and other weather-related variables on *Cryptosporidium* and *Giardia* in fresh surface waters

Ian Young, Ben A. Smith and Aamir Fazil

ABSTRACT

Global climate change is expected to impact drinking water quality through multiple weather-related phenomena. We conducted a systematic review and meta-analysis of the relationship between various weather-related variables and the occurrence and concentration of *Cryptosporidium* and *Giardia* in fresh surface waters. We implemented a comprehensive search in four databases, screened 1,228 unique citations for relevance, extracted data from 107 relevant articles, and conducted random-effects meta-analysis on 16 key relationships. The average odds of identifying *Cryptosporidium* oocysts and *Giardia* cysts in fresh surface waters was 2.61 (95% CI = 1.63–4.21; I^2 = 16%) and 2.87 (95% CI = 1.76–4.67; I^2 = 0%) times higher, respectively, during and after extreme weather events compared to baseline conditions. Similarly, the average concentration of *Cryptosporidium* and *Giardia* identified under these conditions was also higher, by approximately 4.38 oocysts/100 L (95% CI = 2.01–9.54; I^2 = 0%) and 2.68 cysts/100 L (95% CI = 1.08–6.55; I^2 = 48%). Correlation relationships between other weather-related parameters and the density of these pathogens were frequently heterogeneous and indicated low to moderate effects. Meta-regression analyses identified different study-level factors that influenced the variability in these relationships. The results can be used as direct inputs for quantitative microbial risk assessment. Future research is warranted to investigate these effects and potential mitigation strategies in different settings and contexts.

Key words | climate change, *Cryptosporidium*, drinking water, *Giardia*, meta-analysis, systematic review

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INTRODUCTION

Global climate change is expected to impact water quality through multiple processes, including gradual temperature increases, changes in seasonal and weather patterns, and increased frequency and intensity of extreme weather events such as excess rainfall, floods, and droughts (Ebi *et al.* 2006; Semenza *et al.* 2012a; Cann *et al.* 2013; Schijven *et al.* 2013). The protozoan pathogens *Cryptosporidium* and *Giardia* are particularly sensitive to these changes due to their environmentally mediated life cycle (Lal *et al.* 2013). Characteristics of these pathogens such as their prolonged survival in the environment, transmission through drinking and recreational water sources, resistance to chlorine disinfection, and low infectious dose contribute to their significant health threat, especially in vulnerable populations such as the immunocompromised (Savioli *et al.* 2006; King & Monis 2007; Lal *et al.* 2013).

Sporadic cases and outbreaks of cryptosporidiosis and giardiasis have been linked to various weather-related factors that may be affected by climate change (MacKenzie *et al.* 1994; Curriero *et al.* 2001; Thomas *et al.* 2006; Jagai

doi: 10.2166/wh.2014.079

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et al. 2009; Lal et al. 2012; Cann et al. 2013). For example, a recent systematic review found a consistent, seasonal increase of cryptosporidiosis and giardiasis in temperate, developed countries during the summer months (Lal et al. 2012), and a meta-analysis of global cryptosporidiosis cases identified an increased incidence associated with seasonal air temperature and precipitation patterns (Jagai et al. 2009). These associations may be affected by various ecological processes, including prolonged seasonal periods suitable for (oo)cyst transmission and increased contamination of drinking water sources due to excess rainfall and storm water runoff, the latter of which could also compromise the efficacy of water treatment plant filtration and disinfection measures (Kistemann et al. 2002; King & Monis 2007; Cizek et al. 2008; Tryland et al. 2011; Lal et al. 2013).

Quantitative microbial risk assessment (QMRA) models can be used to characterize and predict the risks of illness due to *Cryptosporidium*, *Giardia*, and other pathogens under various climate change scenarios in order to inform risk management and decision-making about potential mitigation and adaptation strategies (Schijven et al. 2013; Smith et al. 2004). In Canada, a predictive modeling framework that includes several QMRA model case studies was developed to project the potential effects of climate change and adaptation measures on food and water safety (Smith et al. in press). One of these case studies estimated risks from climate change impacts on *Cryptosporidium* and *Giardia* contamination of drinking water in a northern community (Smith et al. in press). Structured and transparent knowledge synthesis methods can inform the driving relationships in this model with credible and robust inputs regarding the potential impact of climate change on *Cryptosporidium* and *Giardia* contamination of fresh surface waters (European Food Safety Authority (EFSA) 2010; Rajić & Young 2013).

A systematic review is a knowledge synthesis method used to identify, critically appraise, and integrate published research evidence about a clearly defined topic, and meta-analysis is a statistical method that can be used to combine data from multiple individual studies identified in a systematic review (EFSA 2010; Higgins & Green 2011; Rajić & Young 2013). Systematic reviews and meta-analyses are widely considered the most reliable sources of research evidence to inform risk analysis and decision-making because results are more precise and have a lower risk of bias compared to individual primary research studies (EFSA 2010; Higgins & Green 2011; Rajić & Young 2013). In addition, they use more transparent and replicable methods than traditional, ad hoc literature reviews (Waddell et al. 2009). For these reasons, there is increasing international momentum to integrate systematic review and meta-analysis methods with QMRA and other decision-analysis tools for food and water safety (EFSA 2010; Rajić & Young 2013). The purpose of this study was to conduct a systematic review and meta-analysis of the effects of weather-related variables potentially affected by climate change on the occurrence and concentration of *Cryptosporidium* oocysts and *Giardia* cysts in fresh surface waters. The primary objective was to quantify estimates of the association between key weather-related variables and these pathogens to inform climate change adaptation QMRA models.

METHODS

Review question and scope

We conducted the systematic review in accordance with a protocol that was developed *a priori* and contained details on the review methods and procedures described herein, including screening and extraction forms (EFSA 2010; Higgins & Green 2011; Rajić & Young 2013). Our review question was: 'What are the relationships between extreme weather events and other key weather-related variables and the occurrence and density of *Cryptosporidium* oocysts and *Giardia* cysts in fresh surface waters?' The review was conducted as one of two complementary systematic reviews to inform QMRA model case studies considered during the development of a risk modeling framework (Smith et al. in press). Therefore, the review screening and extraction forms were developed to assess a range of other review questions relevant to the framework.

Search strategy

We developed a search algorithm by extracting key terms from the titles and abstracts of 10 potentially relevant articles identified *a priori*. Terms were combined in a reproducible search algorithm that was pre-tested in Scopus and designed to

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capture all 10 pre-identified articles. The final algorithm contained combinations of terms in the following categories: weather-related variables (temperature OR rainfall OR rain OR run-off OR runoff OR snowmelt OR precipitation OR climate OR weather OR storm* OR flood* OR turbidity); pathway (water); and pathogen (*Cryptosporidium* OR *Giardia*). Searches were implemented on July 25, 2013, in Scopus, PubMed, Environmental Sciences and Pollution Management, and CAB Direct (containing the sub-databases Animal Health and Production Compendium, Aquaculture Compendium, Crop Production Compendium, Forestry Compendium, and CAB Abstracts). The final database-specific search algorithms are available as Supplementary material (available online at http://www.iwaponline.com/wh/013/079.pdf).

We also conducted a search for gray literature (e.g., theses and research reports) using the Scopus web search feature on the same date and using the same search algorithm described above. For pragmatic reasons, we searched only the first 100 of these hits that were automatically sorted by relevance by the search platform. To identify any additional relevant articles potentially missed by the search, we reviewed the references lists of the 20 most recently published relevant articles and 10 related literature reviews (list of articles available as Supplementary material). The search strategy was developed with the assistance of an information specialist.

Relevance screening

The titles and abstracts of all identified citations were screened for relevance using a structured form that was developed *a priori* (Supplementary material). The form contained one key inclusion question to determine whether citations described primary research investigating the relationship between weather-related variables potentially affected by climate change and the occurrence or concentration of *Cryptosporidium* oocysts or *Giardia* cysts in fresh surface waters. Relevant weather-related variables included extreme weather events (e.g., storms and heavy rainfall), precipitation, air and water temperature, water turbidity and flow rate, relative humidity, wind speed, cloud coverage, and sunlight exposure (Semenza *et al.* 2012b). Citations were excluded if they did not describe any of these variables, if they described intervention research (e.g., treatments to reduce protozoan contamination of water sources), if the research was not conducted under field conditions, or if they described research investigating only non-water sources or marine, brackish, groundwater, raw wastewater, or treated water sources.

Article characterization and data extraction

Potentially relevant articles were procured and confirmed for relevance using an article characterization and data extraction form developed *a priori* (Supplementary material). The form contained 23 questions about article and study characteristics, including publication date; study location; study design; sampling and laboratory procedures; weather-related variables, pathogens, and sample types investigated; and risk-of-bias and reporting criteria. The form also included a separate section for extraction of quantitative outcome data reflecting the relationships between any of the weather-related variables of interest and *Cryptosporidium* oocysts or *Giardia* cysts in fresh surface waters. Articles in languages other than English, French, or Spanish were excluded due to limited resources for translation.

Review management

All citations identified through searches were entered into the online reference manager RefWorks (Thomson ResearchSoft, Philadelphia, PA) and duplicates were removed using the automatic function and manually. Unique citations were then imported into the web-based, systematic review software program DistillerSR (Evidence Partners, Ottawa, ON) for screening, characterization, and extraction. The forms used for relevance screening and article characterization were pre-tested on a selection of 30 abstracts and five articles, respectively. Reviewing proceeded only when consistent inclusion and exclusion agreement was achieved between reviewers (kappa >0.8). All stages of reviewing were performed by two independent reviewers. Discrepancies or conflicts between reviewers were resolved by consensus.

Meta-analysis

Random-effects meta-analysis was conducted on unique data subsets with sufficiently reported and comparable

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outcomes from ≥2 articles in the following three summary formats: prevalence data; concentration data; and correlation data. A total of four meta-analyses were conducted on prevalence and concentration data subsets reflecting the difference between the occurrence (presence/absence) and density ([oo]cysts/100 L), respectively, of *Cryptosporidium* oocysts and *Giardia* cysts identified during extreme weather events (e.g., excess precipitation or storm water runoff) compared to baseline (e.g., normal or dry) weather conditions. The specific definition and criteria for an extreme weather event differed by study. Prevalence data were extracted in a 2×2 table format (i.e., number of positive and negative samples in each group) and meta-analysis was conducted on the odds ratio (OR) effect measure. Concentration data were analyzed as a raw mean difference (MD) in protozoan counts. A total of 12 meta-analyses were also conducted on Spearman rank and Pearson correlations reflecting associations between the density of *Cryptosporidium* oocysts or *Giardia* cysts and the following weather-related variables: air temperature; water temperature; water turbidity; water flow rate (m^3/s); and precipitation (mm of rainfall within 24 or 72 h of sampling).

All meta-analysis models were developed using the DerSimonian and Laird method (DerSimonian & Kacker 2007). The models did not account for the extra level of variation due to some comparisons being clustered within articles because of the limited number of observations in each data subset. To meet normality assumptions, ORs and MDs and their standard errors (SE) were converted to the natural logarithm scale for analysis and correlation coefficients and their SEs were converted to Fisher's z-scale (Borenstein *et al.* 2009). For prevalence data, zero values were replaced with a standard continuity correction of 0.5 prior to analysis (Borenstein *et al.* 2009; Higgins & Green 2011). Raw sampling data for correlation relationships of interest, where reported, were extracted and a Spearman rank correlation was calculated post hoc. For these data, non-detectable concentrations for pathogens were replaced with zero values (McGuire *et al.* 2002).

For concentration data, *Cryptosporidium* oocysts and *Giardia* cysts were not detected in 20 and 25% of observations, respectively, in one of the comparison groups; therefore, a constant value of 1.00001 was added to these datasets before the logarithmic transformation to allow inclusion of all comparisons. A sensitivity analysis was conducted on these results by comparing the meta-analysis findings to an analysis that excluded comparisons with zero counts. In addition, for comparison purposes, we conducted a meta-analysis of concentration data using a random-effects Poisson regression model (Bagos & Nikolopoulos 2009). In these models, protozoan counts in (oo) cysts/100 L from each study were treated as incidence rate data, with average effect estimates calculated as incidence rate ratios (Bagos & Nikolopoulos 2009). The models included a dichotomous indicator variable to represent the exposure effect (1 = extreme weather event and 0 = baseline conditions) and a random coefficient for the study comparison. These models were conducted using the methods described by Bagos & Nikolopoulos (2009).

Heterogeneity in the meta-analyses was assessed using the Q statistic chi-squared test and I^2 (Higgins *et al.* 2003; Borenstein *et al.* 2009). Heterogeneity was considered significant if *P*-values for the Q-test were <0.10 or if I^2 values were >25% (Higgins *et al.* 2003; Borenstein *et al.* 2009). A sign test was also applied to determine whether relationships showed a consistent positive or negative association, with $P < 0.05$ indicating a significant direction of effect (Borenstein *et al.* 2009). Average estimates of effect were reported only if heterogeneity was not significant, or if the sign test indicated a consistent direction of effect in cases of significant heterogeneity. Begg's adjusted rank correlation and Egger's regression tests were used to test for possible publication bias on meta-analysis data subsets with ≥10 comparisons and when heterogeneity was not significant (Sterne *et al.* 2011). For these tests, $P < 0.05$ was considered significant. All meta-analyses were conducted using Comprehensive Meta-Analysis 2.0 (Biostat Inc., Englewood, NJ), except for the Poisson regression analyses, which were conducted using GLLAMM in Stata 10 (StataCorp, College Station, TX).

Meta-regression

Meta-regression was conducted on meta-analysis data subsets with $I^2 > 0\%$ and ≥10 comparisons in order to explore possible sources of heterogeneity in the effect estimates across studies (Thompson & Higgins 2002). The

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following nine pre-specified variables were evaluated as potential covariates in meta-regression models: article type (journal article vs. other); publication year (continuous); study region (North America vs. other); study design (cross sectional vs. longitudinal); water source type (river/stream waters vs. lake/reservoir/other); water sampling location (municipal/multiple locations vs. open water source/watershed); use of the United States (US) Environmental Protection Agency (EPA) Method 1622 or 1623 (yes vs. no) or polymerase chain reaction (PCR) methods (yes vs. no) to identify protozoa; and whether any quantitative outcomes were insufficiently reported to allow for potential meta-analysis (yes vs. no). For meta-analyses of relationships with extreme weather events, an additional dichotomous variable representing the criteria for an 'extreme weather event' (excess water flow vs. excess precipitation-based/other) was created and evaluated. In addition, a dichotomous variable representing the correlation method (Spearman vs. Pearson) was created and evaluated in analyses with correlation coefficient outcomes. Given the limited number of observations in each meta-analysis subset, all covariates except publication year were modelled as dichotomous variables, and only univariable meta-regression models were evaluated. For each data subset, Spearman rank correlations were used to evaluate collinearity between covariates prior to conducting meta-regression; if evidence of collinearity was identified ($\rho \geq 0.8$), only one of the correlated variables was selected and considered for meta-regression based on its biological relevance. Covariates were considered significant if 95% confidence intervals (CI) excluded the null. Meta-regression was conducted using Stata 10.

Quality-of-evidence assessment

Each meta-analysis data subset was assessed for its overall quality-of-evidence using a modified version of the Cochrane Collaboration's Grades of Recommendation, Assessment, Development and Evaluation (GRADE) approach (Guyatt *et al.* 2011; Higgins & Green 2011; Wilhelm *et al.* 2012). We used an adapted version of the GRADE approach reported by Wilhelm *et al.* (2012), which included an assessment of each of the following five criteria: individual study risk-of-bias and reporting criteria; inconsistency of direction of findings; imprecision of effect estimates; indirectness of individual study measurements; and risk of publication bias. In contrast to the Cochrane Collaboration's recommended approach for intervention research, we did not employ automatic downgrading of observational study designs (nor did we consider potential upgrading of evidence) given the nature of the review question and focus and because all included research was observational (Guyatt *et al.* 2011; Higgins & Green 2011; Wilhelm *et al.* 2012). Datasets started with four points, and points were deducted based on the criteria described in Table 1. The final GRADE rating corresponded to the remaining number of points: one = very low; two = low; three = moderate; four = high.

RESULTS

Characteristics of relevant articles

A total of 1,228 unique citations were identified and screened for relevance, of which 165 were procured and characterized, and 107 were confirmed as relevant (Figure 1). The characteristics of the relevant articles are shown in Table 2, and a citation list of these articles is available as Supplementary material (available online at http://www.iwaponline.com/wh/013/079.pdf). The median publication year among relevant articles was 2006 (range 1988–2013). Most of the 107 relevant articles reported on observational studies conducted in North America (37%) and that used a longitudinal sampling design (71%). The risk-of-bias and reporting criteria of the 107 relevant articles are shown in Table 3. Most relevant articles sufficiently reported their sampling methods and procedures (90%), but nearly 70% reported at least some of their quantitative outcomes in a format insufficient for extraction and potential use in meta-analysis (Table 3).

Meta-analysis results

The meta-analysis results are shown in Table 4. The average odds of identifying *Cryptosporidium* oocysts and *Giardia* cysts in fresh water sources was 2.61 and 2.87 times higher, respectively, during and after extreme weather events compared to baseline weather conditions (Table 4). Similarly, the average concentration of

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Journal of Water and Health | 13.1 | 2015

Table 1 | Modified GRADE approach for evaluating the quality-of-evidence of data subsets investigating relationships between weather-related variables and *Cryptosporidium* and *Giardia* in fresh surface waters (adapted from Wilhelm *et al.* 2012)

Criteria	Point deductions	Explanation
1. Individual study risk-of-bias and reporting problems[a]	None present = 0	From the risk-of-bias assessment questions in the article characterization and data extraction form. Criteria are in accordance with recommended reporting guidelines for observational studies (The EQUATOR Network 2013)
a) Insufficient reporting of sampling methods and procedures	≥50% of studies meet any of a) or b) criteria = −1	
b) Insufficient reporting of laboratory methods	≥50% of studies meet both a) and b) criteria = −2	
2. Inconsistency of direction of findings among studies	Not present = 0	Consistency in direction of effect as measured by the sign test. Heterogeneity in the results among included studies as measured by the Q test and I^2
a) Consistent direction of effect, but significant heterogeneity	a) = −1	
b) Inconsistent direction of effect and significant heterogeneity	b) = −2	
3. Imprecision of effect estimates	Not present = 0	Study sample size is less than required to obtain measureable effects, or if sample size calculation not conducted, study includes <50 observations
a) Present in ≥50% of individual studies	a) = −1	
4. Indirectness of individual study sample parameter as representative of target parameter	Not present = 0	Indirectness indicates studies sampled surrogate parameter instead of direct parameter of interest (e.g., measuring rainfall from a surrogate location instead of directly at the sampling site)
a) ≥50% of studies indirectly measure the weather-related variable, sample type or pathogen of interest	a) = −1	
b) ≥50% of studies measure two or more of the above parameters indirectly	b) = −2	
5. Publication bias	Not present = 0	This criterion can only be evaluated if publication bias assessment is possible based on the nature of the data (i.e., ≥10 studies, non-significant heterogeneity, and at least some of the studies have significant results)
a) Present in data subset	a) = −1	

[a]Given the nature of the topic and that all included research was observational in design, these reporting criteria were considered as the most appropriate indicators of the risk-of-bias of included articles in this review.

Cryptosporidium and *Giardia* identified in fresh water sources during and after extreme weather events was approximately 4.38 oocysts/100 L and 2.68 cysts/100 L higher, respectively, compared to baseline conditions (Table 4). The forest plots of the individual study and average estimates of effect for these four relationships are shown in Figures 2–5. Heterogeneity was low and non-significant for both prevalence relationships and for the *Cryptosporidium*–concentration relationship (Table 4), all of which received a moderate GRADE rating. For the association between extreme weather events and *Giardia* concentration, although a consistent, positive direction of effect was identified, the relationship was heterogeneous ($I^2 = 48\%$) and the GRADE rating was low. A sensitivity analysis of the concentration data meta-analyses indicated small changes (<20%) in the effect estimates with a slightly larger MD when comparisons with zero values were excluded (Supplementary material). In addition, the

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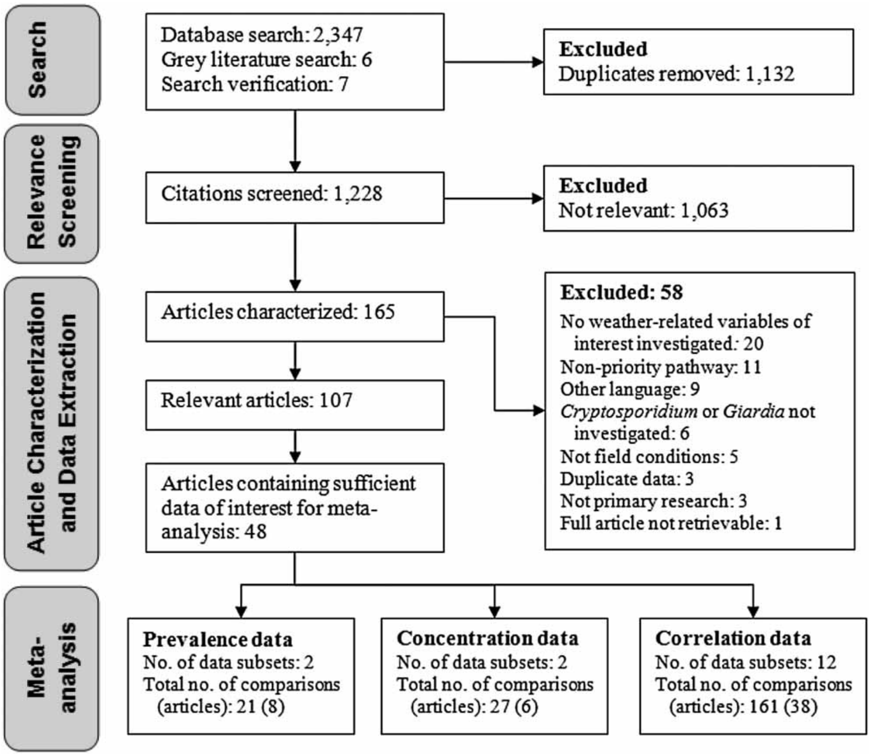

Figure 1 | Systematic review and meta-analysis flow chart.

random-effects Poisson regression approach to meta-analysis for these data showed similar effects (Supplementary material). The results of the correlation meta-analyses are shown in Table 4 and the corresponding forest plots, along with the detailed GRADE assessments for all analyses, are available as Supplementary material. No evidence of publication bias was identified in any of the three data subsets where it was possible to evaluate this bias (Table 4).

Meta-regression results

The results of the meta-regression analyses are shown in Table 5. The odds of identifying *Cryptosporidium* oocysts during or after extreme weather events compared to baseline conditions was 2.82 times higher when sampling was conducted at municipal or multiple locations compared to open water sources or watersheds (Table 5). For the correlation between water turbidity and *Giardia* densities, studies that sampled in municipal or multiple locations reported a higher positive correlation value than those that sampled in open water sources/watersheds, while studies reported in publications other than journal articles (e.g., theses and reports) were more likely to report an opposite, negative correlation (Table 5). Studies that reported using US EPA Methods 1622 or 1623 to identify pathogens were more likely to report a weaker correlation between water turbidity and *Cryptosporidium* density than studies that did not use these methods (Table 5). Studies that reported at least some of their quantitative outcome data in formats insufficient for extraction and potential use in meta-analysis were more likely to report a larger negative correlation between water temperature and *Cryptosporidium* and *Giardia* densities, as well as a larger positive correlation between water flow rate and *Cryptosporidium*, compared to studies that reported all of their outcome data in a sufficient format for extraction (Table 5). No significant covariates were identified for the relationship between extreme weather events and *Giardia* concentration and the correlation between water flow rate and *Giardia* density (Table 5).

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Table 2 | Characteristics of 107 relevant articles investigating relationships between weather-related variables and *Cryptosporidium* and *Giardia* in fresh surface waters

Characteristic	No.	%
Publication year:		
2011–2013	21	19.6
2006–2010	38	35.5
2001–2005	21	19.6
1988–2000	28	26.2
Publication type:		
Journal article	96	89.7
Thesis or dissertation	6	5.6
Research report	2	1.9
Conference proceedings paper	2	1.9
Book	1	0.9
Publication language:		
English	103	96.3
French	2	1.9
Spanish	2	1.9
Study location:		
US/Canada	40	37.4
Europe	28	26.2
Asia	20	18.7
Central/South America	8	7.5
Australia/New Zealand	6	5.6
Africa	5	4.7
Study design:		
Longitudinal/time-series	76	71.0
Cross-sectional	31	29.0
Weather-related variables investigated[a]:		
Water parameters:	81	75.7
Water turbidity	70	65.4
Water temperature	48	44.9
Water flow rate	26	24.3
Other water parameters	65	60.7
Seasonality	46	43.0
Precipitation	39	36.4
Extreme weather event	19	17.8
Air temperature	8	7.5
Other	3	2.8
Water sources investigated[a]:		
Fresh surface waters:	101	94.4
Rivers/streams	93	86.9
Lakes/reservoirs	34	31.8
Drinking water treatment plant effluent	23	21.5
Wastewater treatment plant effluent	11	10.3
Groundwater	12	11.2
Municipal or private tap water	8	7.5
Raw wastewater/sewage	5	4.7
Urban storm sewers	5	4.7
Water storage tanks	5	4.7
Location of water sampling[a]:		
Open water source/watershed	78	72.9
Municipal or private source	61	57.0
Farm streams or runoff	4	3.7
Water source usage[a]:		
Drinking water	84	78.5
Recreational water	13	12.1
Not reported	17	15.9
Outcomes investigated[a]:		
Cryptosporidium oocysts	104	97.2
Giardia cysts	84	78.5
Indicator bacteria	70	65.4
Other enteric pathogens	17	15.9
Laboratory methods[a]:		
Microscopy	99	92.5
US EPA Method 1622/1623	48	44.9
Other	51	47.7
PCR	20	18.7
Not reported	6	5.6

(*continued*)

Table 2 | continued

[a] Multiple selections were possible for these questions, so percentages do not necessarily add to 100%.

DISCUSSION

We identified consistent relationships between the occurrence and concentration of *Cryptosporidium* oocysts and *Giardia* cysts in fresh surface waters during and after extreme weather events compared to baseline weather conditions (Table 4). During these conditions, excessive rainfall and runoff can mobilize pathogens from point and non-point sources and can cause their re-suspension from sediments,

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Table 3 | Risk-of-bias and reporting criteria among 107 relevant articles investigating relationships between weather-related variables and *Cryptosporidium* and *Giardia* in fresh surface waters

Criteria	No.	%
Were sampling methods and procedures adequately reported or referenced to allow replication of the study?		
Yes	96	89.7
No	11	10.3
Were the sampling dates (month/year) reported?		
Yes	83	77.6
No	24	22.4
Was the sampling frequency reported?		
Yes	86	80.4
No	21	19.6
Were laboratory methods for detection of pathogens adequately reported or referenced to allow replication of the study?		
Yes	99	92.5
No	8	7.5
Were the results adjusted for the recovery efficiency of the laboratory testing method?		
Yes	8	7.5
No/not reported	99	92.5
Were outcomes sufficiently reported to allow for extraction and potential use in meta-analysis[a]?		
Yes, at least some outcomes sufficiently reported	60	56.1
No, at least some outcomes insufficiently reported	74	69.2
No, all outcomes insufficiently reported	47	43.9

[a] Multiple selections were possible for these questions, so percentages do not necessarily add to 100%.

contributing to an increased risk of surface water contamination (Atherholt *et al.* 1998; Cizek *et al.* 2008; Duris *et al.* 2013). These relationships did not appear to be dependent on the specific criteria used to define an extreme weather event or the time between event occurrence and pathogen sampling among the included studies. For example, similar findings were found among the studies even though study criteria for extreme weather events were based on various levels of increases in water flow rate, depth, and precipitation accumulation, and sampling occurrences ranged from throughout, during the peak, and immediately after the event (Gibson III *et al.* 1998; Kistemann *et al.* 2002; Signor *et al.* 2005, 2007; Rijal *et al.* 2009). In contrast to these findings, no consistent correlations were identified between precipitation totals within 24 and 72 h of sampling and either pathogen, except for a weak correlation between the latter and *Cryptosporidium* density across three studies (Table 4). This suggests that rainfall accumulation alone is not a reliable indicator of the concentration of *Cryptosporidium* oocysts or *Giardia* cysts in fresh water sources, and a threshold level likely must be exceeded before precipitation has an appreciable impact on these pathogens (Atherholt *et al.* 1998; Curriero *et al.* 2001; Thomas *et al.* 2006; Wilkes *et al.* 2011). Further research is warranted to investigate the prevalence and concentration of these pathogens in fresh surface waters under varying extreme weather conditions and in different locations and contexts.

A small, positive correlation was identified between water turbidity and flow rate and *Cryptosporidium* density, with a weaker association identified between each variable and *Giardia* densities (Table 4). Increasing water turbidity and flow rates can result in increased protozoan densities due to particle association and aggregation and the re-suspension of (oo)cysts from water sediments (Atherholt *et al.* 1998; King & Monis 2007). Research also indicates that while (oo)cysts can survive and maintain their infectivity in low temperature conditions, they are highly susceptible to increasing environmental temperatures (King & Monis 2007; Peng *et al.* 2008). However, although we found a weak, negative correlation between water temperature and *Giardia* densities, we did not identify a consistent relationship between water temperature and *Cryptosporidium* or between air temperature and either pathogen. Therefore, despite being readily measurable, each of these water parameters (temperature, turbidity, and flow rate) has limited universal utility as a potential surrogate measure for *Cryptosporidium* and *Giardia* densities in fresh surface waters given the moderate to low average correlation values and the significant heterogeneity identified across studies. Each of these relationships should be considered context-specific and is likely affected by several meteorological, temporal, hydrological, and geographic factors, as well as methodological differences among studies (Atherholt *et al.* 1998; Kistemann *et al.* 2002; McGuire *et al.* 2002; Brookes *et al.* 2004).

Several factors were identified in meta-regression analyses that explained some of the variability associated with

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Table 4 | Summary of meta-analyses of relationships between selected weather-related variables and *Cryptosporidium* and *Giardia* in fresh surface waters

Outcome/relationship	No. of comparisons (articles)	Q test P-value	I^{2a}	Average estimate of effect (95% CI)[b]	Sign test direction of effect (P-value)	Egger's (Begg's) pub. bias test P-value	GRADE rating[c]
Cryptosporidium							
Extreme weather events – prevalence	13 (8)	0.284	15.8%	OR = 2.61 (1.63, 4.21)	Positive (0.003)	0.192 (0.669)	Moderate
Extreme weather events – concentration	15 (6)	0.527	0%	MD = 4.38 (2.01, 9.54)	Positive (0.006)	0.574 (1.000)	Moderate
Air temperature – correlation	4 (4)	0.002	80.5%	N/a	No association (0.500)	N/a	Very low
Water temperature – correlation	16 (15)	<0.001	83.0%	N/a	No association (0.244)	N/a	Very low
Water turbidity – correlation	40 (33)	<0.001	82.1%	$r = 0.37$ (0.27, 0.46)	Positive (<0.001)	N/a	Low
Water flow rate – correlation	14 (11)	<0.001	73.2%	$r = 0.35$ (0.24, 0.46)	Positive (0.002)	N/a	Low
Precipitation (24 h prior) – correlation	5 (5)	0.227	29.1%	$r = -0.01$ (−0.09, 0.07)	No association (0.625)	N/a	Low
Precipitation (72 h prior) – correlation	3 (3)	0.781	0%	$r = -0.18$ (−0.23, −0.12)	No association (0.250)	N/a	Moderate
Giardia							
Extreme weather events – prevalence	8 (4)	0.675	0%	OR = 2.87 (1.76, 4.67)	Positive (0.008)	N/a	Moderate
Extreme weather events – concentration	12 (4)	0.032	47.8%	MD = 2.68 (1.08, 6.55)	Positive (0.032)	N/a	Low
Air temperature – correlation	4 (4)	0.078	55.9%	N/a	No association (0.750)	N/a	Very low
Water temperature – correlation	14 (13)	<0.001	79.6%	$r = -0.27$ (−0.42, −0.12)	Negative (0.011)	N/a	Low
Water turbidity – correlation	35 (28)	<0.001	78.4%	$r = 0.22$ (0.11, 0.32)	Positive (0.011)	N/a	Low
Water flow rate – correlation	14 (11)	0.155	28.0%	$r = 0.19$ (0.12, 0.26)	Positive (0.044)	0.755 (0.783)	Moderate
Precipitation (24 h prior) – correlation	7 (7)	0.001	74.3%	N/a	No association (0.328)	N/a	Very low
Precipitation (72 h prior) – correlation	4 (4)	<0.001	90.5%	N/a	No association (0.500)	N/a	Very low

CI = confidence interval; OR = odds ratio; MD = mean difference; N/a = not applicable.

[a]I^2 refers to the percentage of variation in effect estimates across study comparisons that is due to heterogeneity rather than sampling error.

[b]Reported estimates of effect have been back-transformed to their original scale: OR for prevalence data, MD in (oo)cysts/100 L for concentration data, and r for correlation data. The back-transformed MD values should be considered only approximations due to the addition of a constant value of 1.00,001 to the original dataset to incorporate zero values.

[c]The explanation of the GRADE ratings is as follows (Guyatt *et al.* 2011; Higgins & Green 2011):

Very low = the true effect is likely to be substantially different from the measured estimate of effect;
Low = the true effect may be substantially different from the measured estimate;
Moderate = the true effect is likely to be close to the measured estimate, but there is a possibility that it is substantially different;
High = strong confidence that the true effect lies close to that of the measured estimate.

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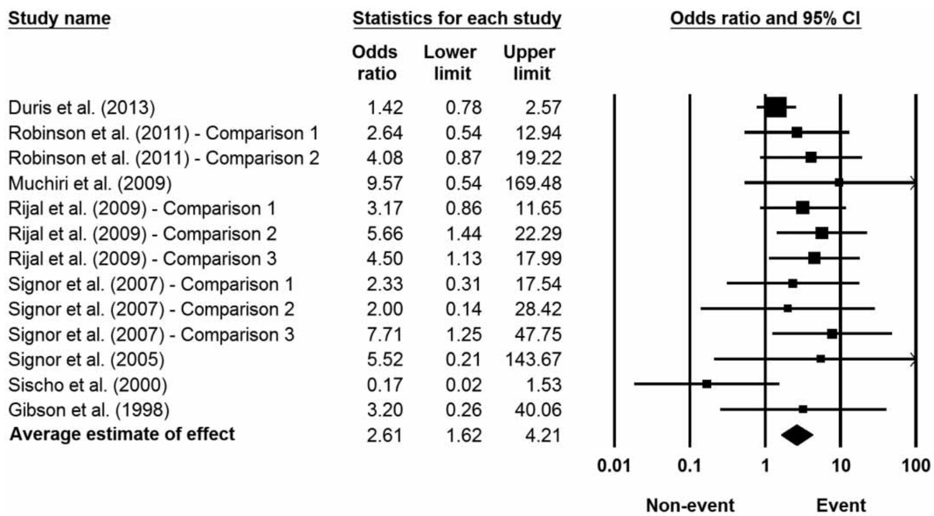

Figure 2 | Random-effects meta-analysis of the relationship between extreme weather events and the prevalence of *Cryptosporidium* oocysts in fresh surface waters. Note that the upper confidence interval exceeds the forest plot scale for some studies. Full citations of studies referenced in this figure are available in the Supplementary material (available online at http://www.iwaponline.com/wh/013/079.pdf). CI = confidence interval.

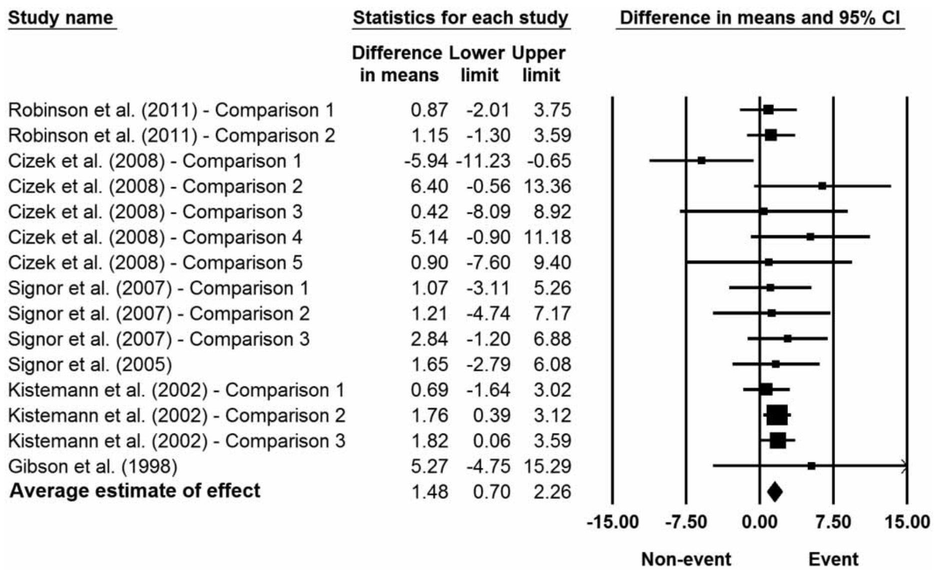

Figure 3 | Random-effects meta-analysis of the relationship between extreme weather events and the concentration (oocysts/100 L) of *Cryptosporidium* oocysts in fresh surface waters. The MDs in this figure are shown in the natural logarithm scale. Note that the upper confidence interval exceeds the forest plot scale for one study. Full citations of studies referenced in this figure are available in the Supplementary material (available online at http://www.iwaponline.com/wh/013/079.pdf). CI = confidence interval.

the average estimates of effect for various meta-analysis relationships. For example, studies that sampled in municipal or multiple locations compared to open water sources and watersheds were more likely to report stronger relationships between extreme weather events and *Cryptosporidium* prevalence and water turbidity and *Giardia* density. Many studies that sampled in municipal locations investigated pathogens in combined sewer overflows and other urban waterways, which can be heavily contaminated from untreated sewage and stormwater discharges during extreme weather events (Gibson III *et al.* 1998; Arnone & Walling 2006; Schets *et al.* 2008; Duris *et al.* 2013), and it is possible that these relationships are more pronounced in these situations. In contrast, many open source watersheds are influenced by mixed geographic and land use factors with many non-point sources of contamination (Wilkes *et al.*

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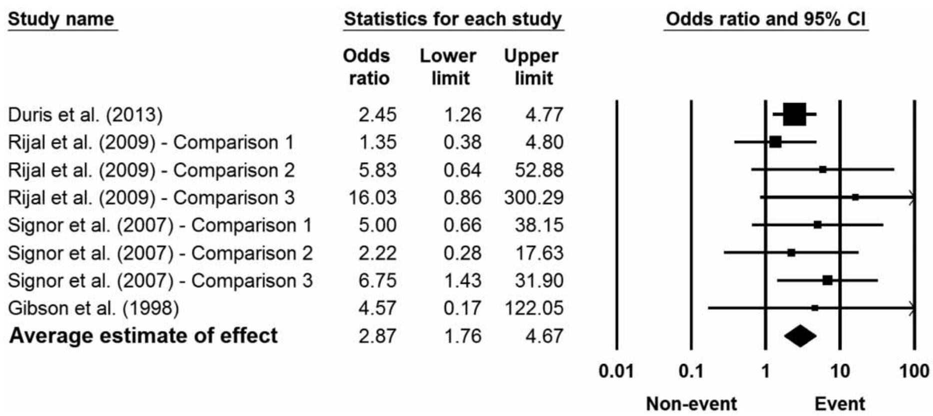

Figure 4 | Random-effects meta-analysis of the relationship between extreme weather events and the prevalence of *Giardia* cysts in fresh surface waters. Note that the upper confidence interval exceeds the forest plot scale for some studies. CI = confidence interval.

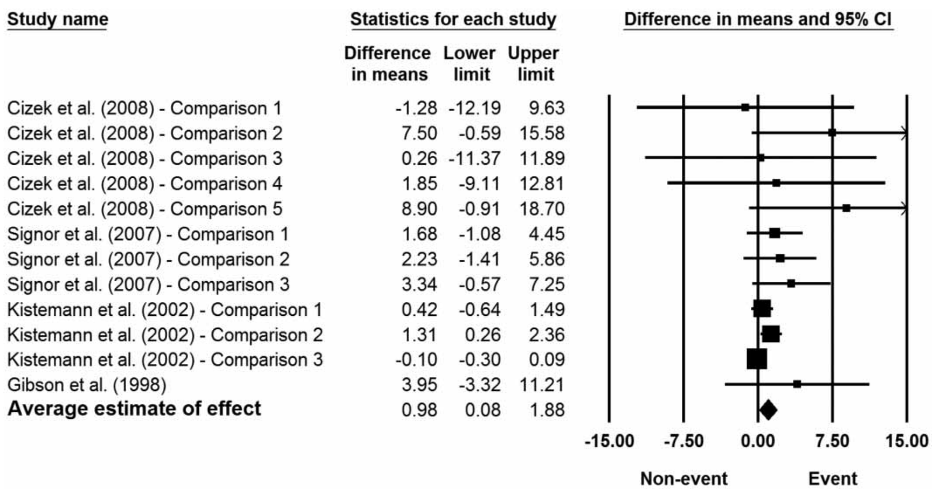

Figure 5 | Random-effects meta-analysis of the relationship between extreme weather events and the concentration (cysts/100 L) of *Giardia* cysts in fresh surface waters. The MDs in this figure are shown in the natural logarithm scale. Note that the upper confidence interval exceeds the forest plot scale for some studies. CI = confidence interval.

2011; Duris *et al.* 2013). The average correlation between water turbidity and *Giardia* density across study comparisons also differed depending on the article publication type, with positive correlations more likely to be reported in journal articles compared to other documents (e.g., reports and theses). This may reflect a publication bias effect, similar to that reported in the health sector, where a systematic review found that clinical trials reporting positive and significant results were more likely to be published in peer-reviewed journals than studies reporting negative or non-significant findings (Hopewell *et al.* 2009). This finding underscores the importance of including gray literature documents in systematic reviews to ensure a more accurate representation of the overall state of evidence on a topic.

Heterogeneity in the correlation between water turbidity and *Cryptosporidium* density was partially explained by the reported use of US EPA Methods 1622 or 1623 to detect the protozoa compared to other approaches. These methods are the most widely recognized and used approaches for detecting *Cryptosporidium* and *Giardia* in surface waters (US EPA 2005a, 2005b; Yang *et al.* 2008; Health Canada 2012). Other approaches have been shown to have lower recovery efficiencies and increased variability compared to the US EPA methods (Quintero-Betancourt *et al.* 2002); however, the EPA methods also have limitations with variable recovery efficiencies, they cannot determine host species of origin or the viability or infectivity of (oo)cysts, and there are logistical challenges when implementing these methods in

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Table 5 | Meta-regression results for eight meta-analyses of relationships between selected weather-related variables and *Cryptosporidium* and *Giardia* in fresh surface waters

Model outcome/relationship	Significant covariates	No. of comparisons (articles)	Coefficient (95% CI)[a]	I^2
Cryptosporidium				
Extreme weather events – prevalence	Sample location (municipal/multiple vs. open water source/watershed)	13 (8)	OR = 2.82 (1.16, 6.89)	0%
Water temperature – correlation	Insufficient reporting of some outcome data (yes vs. no)	16 (15)	$r = -0.40$ (-0.67, -0.04)	74.1%
Water turbidity – correlation	Use of US EPA Methods 1622/1623 vs. other	40 (33)	$r = -0.24$ (-0.43, -0.04)	78.8%
Water flow rate – correlation	Insufficient reporting of some outcome data (yes vs. no)	14 (11)	$r = 0.41$ (0.22, 0.57)	25.0%
Giardia				
Extreme weather events – concentration	None significant	12 (4)	N/a	N/a
Water temperature – correlation	Insufficient reporting of some outcome data (yes vs. no)	14 (13)	$r = -0.38$ (-0.62, -0.06)	66.8%
Water turbidity – correlation	Sample location (municipal/multiple vs. open water source/watershed)	35 (28)	$r = 0.29$ (0.06, 0.49)	78.6%
	Article type (other vs. journal article)	35 (28)	$r = -0.51$ (-0.73, -0.17)	77.1%
Water flow rate – correlation	None significant	14 (11)	N/a	N/a

CI = confidence interval; OR = odds ratio; N/a = not applicable.
[a]Reported coefficients have been back-transformed to their original scale: OR for prevalence data and r for correlation data.

practice (Weintraub 2006; Yang *et al.* 2008; Health Canada 2012). Further research is needed to develop more accurate, cost-effective, and rapid laboratory methods to detect and enumerate viable and infectious (oo)cysts in fresh water sources.

Articles that reported at least some of their quantitative outcome data in formats insufficient for extraction and potential use in meta-analysis were more likely to report stronger correlations between water flow rate and *Cryptosporidium* densities and between water temperature and both *Cryptosporidium* and *Giardia*. This finding might reflect a selective outcome reporting bias, meaning that authors of these studies could have selectively omitted some of their results due to a lack of statistical significance, lack of perceived importance, or for other reasons (Chan & Altman 2005; Higgins & Green 2011). For example, a review of clinical trials indexed in PubMed in December 2000, and a complementary survey of their authors found that insufficiently reported outcomes were more likely to be non-significant than fully reported outcomes (Chan & Altman 2005). Therefore, reported meta-analyses for the above relationships may have overestimated the average correlation, and the results should be interpreted with caution. This finding highlights the need for primary research authors to report or make available all outcomes regardless of their statistical significance or magnitude of effect. Recent reporting guidelines for primary research and increasing opportunities for authors to provide online supplementary material should help to improve outcome data reporting in the future (The EQUATOR Network 2013).

The results of the correlation meta-analyses indicate that there is no single weather-related variable that is a sufficient indicator of *Cryptosporidium* or *Giardia* densities in fresh surface waters. These results correspond to previous research which indicates that there is also no single indicator organism (e.g., *Escherichia coli*) or other environmental variable that is a reliable surrogate for these pathogens across different water sources and settings (Brookes *et al.* 2004; Wilkes *et al.* 2009; Nieminski *et al.* 2010; Wu *et al.* 2011). Despite the significant resource requirements for *Cryptosporidium* and *Giardia* monitoring among drinking water facilities, particularly for smaller systems (Nieminski *et al.* 2010), enhanced

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surveillance of these pathogens is warranted during and after extreme weather events in order to reliably determine risks of contamination. However, given the time delay between protozoan sampling and laboratory detection, early warning systems and QMRA modeling are also necessary to facilitate the rapid identification and assessment of increased risks of drinking water contamination with *Cryptosporidium* and *Giardia* and to ensure that effective and timely risk mitigation strategies can be implemented. The results of this study can inform these types of preventive approaches.

A holistic and multi-barrier approach should be followed to prevent and mitigate the potential impacts of climate change on *Cryptosporidium* and *Giardia* contamination of fresh surface waters (Health Canada 2012). This should include enhanced watershed protection against the effects of increasingly frequent and intense extreme weather events. For example, vegetated and grassland buffers have been shown to be an effective approach to reducing *Cryptosporidium* contamination of surface water sources from agricultural runoff (Tate *et al.* 2004; Atwill *et al.* 2006). Improvements to stormwater management and the infrastructure and capacity of drinking water facilities could also mitigate the impacts of extreme weather events, particularly for smaller systems with inadequate filtration and disinfection measures. Other risk mitigation strategies could include limiting the uptake of surface water, issuing boil-water advisories, or using additional barriers (e.g., enhanced filtration or treatment) during and immediately after extreme weather events (Health Canada 2012). Further evaluation of these and other mitigation and adaptation strategies is warranted (Smith *et al.* in press).

It is possible that some potentially relevant articles were not included in this review because they were not indexed within the bibliographic databases included in our initial search. Moreover, a more comprehensive search of additional sources of gray literature (e.g., using search engines such as Google or by contacting and searching the websites of targeted organizations) could have yielded additional data. We attempted to minimize this potential bias through our search verification strategy of hand-searching the reference lists of a selection of relevant articles and reviews. A related limitation is that we were only able to review articles in English, French, and Spanish languages. The impact of excluding a small number ($n = 9$) of potentially relevant articles in other languages is unknown.

Meta-analyses were based on data from all identified species of *Cryptosporidium* and *Giardia*. However, previous studies have found that the majority of identified (oo)cysts in fresh water sources are non-viable and non-infectious to humans (Yang *et al.* 2008; Van Dyke *et al.* 2012), and it is unknown whether the relationships characterized in this review would also apply similarly to viable and infectious species. Increased application of PCR-based and molecular detection methods is necessary in future research to differentiate pathogenic from non-pathogenic species and to aid in tracking sources of contamination. In addition, most analyses were based on a small number of comparisons, and several were significantly heterogeneous; therefore, our results should be interpreted appropriately. It is possible that some of the significant covariates in meta-regression analyses could reflect spurious findings, or conversely, that some included variables were not identified as significant due to low power. The dynamics of each relationship investigated in this review are also likely related to other, site-specific factors that might not have been measured or accounted for in the meta-regression models (Atherholt *et al.* 1998; Kistemann *et al.* 2002; McGuire *et al.* 2002; Wilkes *et al.* 2011).

One of the primary aims of this study was to identify and synthesize data on the relationships between extreme weather events and other weather-related variables and the occurrence and concentration of *Cryptosporidium* and *Giardia* in fresh surface waters to inform QMRA models. Reported MDs and ORs (converted to relative risk ratios) from meta-analysis can be integrated into QMRAs alongside other model elements (e.g., initial levels of protozoan contamination, use of water treatments and interventions, and population vulnerabilities) to evaluate the impact of extreme weather events on surface water contamination, and consequently, public health. Changes to frequencies of extreme weather events as projected by climate change models can be simulated to estimate the relative impacts of climate change on public health compared to historic or current conditions (Smith *et al.* in press). The meta-analyses of correlations with other weather-related variables allowed for improved understanding of potential weather-related indicators for *Cryptosporidium* and *Giardia* contamination of

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fresh surface waters. Our results indicated that none of these variables were strong and reliable indicators; therefore, researchers should prioritize the impacts of extreme weather events for QMRA models to estimate the possible effects of weather and climate change on protozoan contamination of fresh surface waters.

CONCLUSION

We used systematic and transparent methods to synthesize the available research knowledge on the relationship between key weather-related variables and *Cryptosporidium* and *Giardia* in fresh surface waters. Random-effects meta-analysis of study outcomes indicated that the average prevalence and concentration of both pathogens was higher when sampling was conducted during or immediately after extreme weather events compared to baseline conditions; these results can be used as credible and reliable inputs for QMRA models of the impact of climate change adaptation on the risks of cryptosporidiosis and giardiasis in humans. Meta-analyses of correlations indicated that there is no single weather-related variable that is a reliable and universal predictor of either pathogen in fresh surface waters. Further research is warranted to investigate these effects and potential risk prevention and mitigation strategies in different contexts and settings.

ACKNOWLEDGMENTS

We thank Janet Harris for assistance developing the search strategy, Brennan Chapman for article procurement, Ashley Farrar for relevance screening and data extraction, and Lisa Waddell and Dr Javier Sanchez for statistical advice. This study was funded by the Public Health Agency of Canada under the 'Adaptation to Climate Change Program'.

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First received 24 March 2014; accepted in revised form 24 July 2014. Available online 2 September 2014

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