Time series study of weather, water quality, and acute gastroenteritis at Water Safety Plan implementation sites in France and Spain

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ABSTRACT

Water Safety Plans (WSPs), recommended by the World Health Organization since 2004, can help drinking water suppliers to proactively identify potential risks and implement preventive barriers that improve safety. Few studies have investigated long-term impacts of WSPs, such as changes in drinking water quality or public health; however, some evidence from high-income countries associates WSP implementation with a reduction in diarrheal disease. To validate the previously observed linkages between WSPs and health outcomes, this time series study examined site-specific relationships between water-related exposures and acute gastroenteritis rates at three locations in France and Spain, including the role of WSP status. Relationships between control or exposure variables and health outcomes were tested using Poisson regression within generalized additive models. Controls included suspected temporal trends in disease reporting. Exposures included temperature, precipitation, raw water quality, and finished water quality (e.g., turbidity, free chlorine). In France, daily acute gastroenteritis cases were tracked using prescription reimbursements; Spanish data aggregated monthly acute gastroenteritis hospital visits. The models identified several significant relationships between indicators of exposure and acute gastroenteritis. Lag times of 6–9 days (including transit time) were most relevant for hydrological indicators (related to precipitation, runoff, and flow) at the two French sites, indicative of viral pathogens. Flush events (defined as surface runoff after a two-week antecedent dry period) linked to nonpoint source pollution were associated with a 10% increase in acute gastroenteritis rates at one location supplied by surface water. Acute gastroenteritis rates were positively associated with elevated turbidity average or maximum values in finished water at locations supplied by both surface and groundwater, by about 4% per 1-NTU increase in the two-week moving average of daily maxima or about 10% per 0.1 NTU increase in the prior month's average value. In some cases, risk appeared to be mitigated by WSP-related treatment interventions. Our results suggest drinking water exposure is associated with some potentially preventable gastrointestinal illness risk in high-income regions.

1. Introduction

Diarrheal disease poses a substantial health burden in many regions of the world, and is a leading cause of death in low-income countries with poor access to safe water, sanitation, and medical care (Troeger et al., 2017). Episodes of acute infectious diarrhea are also common in high income regions, contributing to healthcare costs and lost worker productivity (Hutton and Haller, 2004). Estimates of the burden of acute gastrointestinal illness attributable to drinking water in high-income countries hover around 12% (Colford et al., 2006). Still, public officials in high-income countries may not perceive drinking water

quality as a prominent risk to health, despite the preventable nature of the disease, aging infrastructure, and periodic high-profile outbreaks. Historically, the infrastructure-heavy nature of the sector and technical industry culture have tended to favor reactive management approaches (Takala and Heino, 2017). A dense regulatory environment may further reduce willingness to develop site-specific water quality programs (Amjad et al., 2016).

Proactive risk management for drinking water supplies in all nations has been recommended since 2004 by the World Health Organization (WHO) Guidelines for Drinking Water Quality and the Bonn Charter for Safe Drinking Water (IWA, 2004; WHO, 2004). Risk management

programs such as Water Safety Plans (WSPs) offer a potential pathway to reduce public health risks (Bartam et al., 2009). WSPs seek to emphasize proactive process controls in drinking water production, where end product testing simply verifies effectiveness of the risk management measures. Such programs were first legally required in Iceland beginning in 1995 (Gunnarsdottir et al., 2015) and have since been implemented in more than 90 countries (WHO and IWA, 2017). Published studies report benefits ranging from improved client satisfaction to reduced gastrointestinal illness rates (Gunnarsdottir et al., 2012a, b; Kot et al., 2015; Kumpel et al., 2016; Setty et al., 2017; String and Lantagne, 2016). Nonetheless, transitioning WSPs into widespread use will require added attention to evidence, context, and facilitation (Kitson et al., 2008).

Two multi-site, multiyear studies reported significant health improvements associated with WSP program implementation in Europe (Gunnarsdottir et al., 2012b; Setty et al., 2017), but did not explore the linkages between drinking water exposures and health outcomes on a daily or monthly timescale. Clarification of the most important contributors to health burdens would aid continued quality improvement efforts among drinking water suppliers and regulators, and elucidate pathways for WSP mechanisms of action. This study builds upon the previous WSP literature by validating links between drinking water exposure and health outcomes as a potential area of intervention in high-income countries. It examines associations between weather, water quality indicators, and health outcomes at three European WSP locations, including how WSP implementation status modified these relationships.

Epidemiological approaches for investigating outcomes of public health interventions include time series studies where the population serves as its own control, corresponding in many ways to case-crossover analysis (Lu and Zeger, 2007). Time series studies have been used to interpret risks related to drinking water in the US, Canada, France, Sweden, Russia, and other high-income locations (Aramini et al., 2000; Beaudeau et al., 2014a, 2014b, 2012; Carlton et al., 2014; Egorov et al., 2003; Gilbert et al., 2006; Tinker et al., 2010; Tornevi and Forsberg, 2016; Zhou et al., 2013). This approach offers a means to characterize the relationship between surrogates for pathogen transmission in drinking water and commonly measured health outcomes, such as diarrheal disease. Because it is an observational approach, it identifies association rather than causation, though guided by theoretical causal mechanisms described in existing literature. Time series studies must be site-specific, as the relevance of common risk indicators (e.g., turbidity) is known to vary depending on source water, climate, geography, water treatment methods, and other factors (De Roos et al., 2017; Tam et al., 2007).

2. Methods

2.1. Site selection and description

This retrospective, observational time series study examined daily or monthly data on weather, water quality, and acute gastroenteritis in France and Spain. Three locations were selected as a nested sample based on health data availability from earlier studies involving 20

Table 2
Time periods of data availability at each study location. Location aliases are retained as a nested sample from an earlier study (Setty et al., 2017).

Location	Data Availability	Data Resolution	Water Safety Plan (WSP) Implementation Period
1	1 Jan 2010 – 31 Oct 2015 (5.8 years)	Daily	1 Jan 2011 – 31 Oct 2011 (10 months)
3	13 Aug 2010 – 31 Dec 2015 (5.4 years)	Daily	13 Nov 2012 – 20 Dec 2013 (13 months)
5	1 Jan 2006 – 31 Dec 2016 (11 years)	Monthly	1 Jan 2008 – 31 Dec 2009 (24 months)

(Loret et al., 2016) and five (Setty et al., 2017) Suez-operated utilities, respectively (Table 1). Each location was served by a single drinking water treatment facility (Table 1) that implemented an ISO 22000-certified WSP during the study period (Table 2). The three locations have different climates and water sources, warranting individual models. Raw water is tested prior to treatment at all sites to inform treatment practices, such as coagulant dosage. In addition, location 5 often switches from surface to groundwater sources, which are less vulnerable to nonpoint source polluted runoff, during heavy rain events. A significant reduction in acute gastroenteritis from before to after WSP certification (relative to a comparison area) was previously found at one location ("location 1"), while no significant change or increased acute gastroenteritis rates were observed at the other two locations (Setty et al., 2017).

"Location 1" in northern France comprises one municipality with complete geographical correspondence to the water service area. The climate regime includes cold winters and hot summers with daily average maximum temperatures between 6 °C and 26 °C and periodic heavy precipitation in spring, summer, and fall. The area is on the outskirts of a large urban center, with a sizeable immigrant population (about 25% in 2013). In 2013, about 26.4% of the population lived below the poverty line (INSEE, n.d.). The primary drinking water source is a large river upstream of the urban center in a residential- and agriculture-dominated watershed with some treated wastewater discharges (Garcia-Armisen and Servais, 2007). Water quality is moderate relative to the other two sites, and treated water quality parameters were generally stable over the study period with an improvement in turbidity and total coliform compliance (Setty et al., 2017). These outcomes matched the observed health improvement.

"Location 3" in southern France comprises four municipalities, each with 20–60% correspondence to the water service area due to cross-connections with other water supplies. Supplementary sources are expected to be equivalent or higher quality groundwater. The climate is oceanic, generally mild, and wetter than location 1 with average temperatures between 11 °C and 27 °C. On average across the four municipalities, 7.1% of the population lived below the poverty line in 2013 (INSEE, n.d.). The public water system was first built in 1850, and draws mainly from high-quality groundwater aquifers. Treatment is streamlined (Table 1) as the source is partially protected. Over the study period, the relatively good water quality degraded somewhat in terms of total coliform, heterotrophic plate count, and turbidity levels

Table 1
Characteristics of study locations including country, population served, water source, and treatment scheme. Location aliases are retained as a nested sample from an earlier study (Setty et al., 2017).

Location	Country	Population served	Water source(s)	Treatment scheme[a]
1	France	43,000	Surface water	Coagulation/sedimentation, rapid sand filtration, ozonation, GAC filtration, utrafiltration, pH stabilization, chlorination
3	France	43,000	Groundwater	Pre-oxidation (Cl_2; ClO_2 prior to 2012), GAC filtration, UV, chlorination
5	Spain	148,000	Surface and groundwater	Pre-oxidation (ClO_2), coagulation/sedimentation, rapid sand filtration, (50% to line 1) ozonation/GAC filtration, (50% to line 2) ultrafiltration/reverse osmosis, remineralization, chlorination

[a] GAC = granular activated carbon.

(Setty et al., 2017). Acute gastroenteritis rates increased from before to after WSP implementation, but were not significantly different from a nearby non-WSP comparison area.

At "location 5" in Spain, two municipalities correspond to the water service area. The climate is intermediate between Mediterranean and humid subtropical, with mild winters and hot summers. Average daily maximum temperatures range from 15 °C to 29 °C. Light precipitation is common throughout the year and becomes slightly heavier in the fall. Although estimates are not available at the municipal level, the proportion of the regional population living below the poverty line is about 24% (Idescat, n.d.). The water supply is an intermittently dry river with variable supplementation from groundwater and, occasionally, desalinated seawater. Multiple contamination sources have been identified in the increasingly developed watershed, including treated wastewater and periodic gasoline storage leaks. Water quality is poor relative to the other study locations, but trihalomethane, total organic carbon, and turbidity levels improved in treated water over the study period (Setty et al., 2017). These water quality improvements did not match the observed significant increase in acute gastroenteritis found among those age 15 and over, relative to a comparison area.

At locations 1 and 3, water typically travels from source to tap within 1–2 days. For location 1, transit time through the treatment plant is 2.3–7.9 h, or 4.7 h on average. Distribution usually requires 3–6 h, but takes up to 24 h in some parts of the system. For location 3, transit time through the treatment plant requires 12–24 h depending on the flow rate. Most transit times in the network are 6–12 h, topping out at about 24 h in the farthest reaches of the system. At location 5, total transit time from source to tap ranges from about a half-day to 10.5 days. Estimated transit time from the river intake to the plant outlet is approximately 6 h, and distribution from the plant outlet to residential taps varies from hours up to 10 days. For longer transit times, rechlorination takes place at storage tanks throughout the distribution network.

2.2. Data compilation

Exposure and control variables of interest were identified via literature review (Table 3). Air temperature can affect multiple modes of disease transmission. Hydrology (including precipitation and river flow) helps to describe transport processes for pathogens, such as nonpoint source pollution of surface waters. Frequently measured water quality parameters relevant to pathogen survival included temperature, turbidity (particle content), UV absorption (an indicator of organic

Table 3
Data availability at each study location (Y = yes, N = no, N/A = not applicable, partial data specified by year).

Variables	Location 1	Location 3	Location 5
Exposure			
Air Temperature	Y	Y	Y
Precipitation	Y	Y	Y
River Flow	Y	N/A	N
Temperature (Raw Water)	N	N	Y
Turbidity (Raw Water)	N	2012-15	Y
UV absorption (Raw Water)	N	N	Y
Turbidity (Finished Water)	N	Y	Y
Free Cl (Finished Water)	N	Y	Y
Daily Flow (Finished Water)	N	2012-15	Y
Amount and % Surface Water	N/A	N/A	Y
Control			
Month/Day/Weekday	Y	Y	Y
Holidays (Work/School)	Y	Y	Y
Dependent			
Acute Gastroenteritis Cases	Y	Y	Y
Population (offset)	Y[a]	Y[a]	Y

[a] Due to reporting delays for locations 1 and 3, extrapolated population data were used for 2015.

matter), and residual free chlorine used for disinfection. Finished water flow may be a proxy for drinking water consumption. Finally, the amount and percentage contribution of surface water is relevant for discerning variable exposure to surface versus groundwater sources at location 5, which may be mixed or used in isolation. Controls addressed potential variability in disease reporting behaviors over time and regular seasonal trends. Since the effects of a changing management regime are likely to emerge over a lengthy implementation period rather than a single time point, we stratified the data by time periods before WSP introduction, from WSP team formation to WSP certification (during), and post-certification (after).

Data were collated from: utility records of water quality and flow sensor readings, calendar and meteorological records for each location (Idescat, n.d.; Meteo France, n.d.), source water monitoring (French Ministry of Ecology Sustainable Development and Energy, n.d.), and public health and population records. Acute gastroenteritis surveillance is based on hospital reporting (ICD-9-CM codes for intestinal infectious diseases 001–009) in Spain, courtesy of Servei Català de la Salut (CatSalut), and an algorithm for processing prescription reimbursement records (e.g., for anti-emetics, antispasmodics, and oral rehydration salts) in France (Bounoure et al., 2011), courtesy of Santé Publique France and the French national health insurance program. Since most cases are treated at home, this public health surveillance data is expected to capture about 33% of total cases in France and about 1–2% in Spain (Bounoure et al., 2011). Use of data from human subjects was approved by the Institutional Review Board (IRB) at the University of North Carolina at Chapel Hill (study #15-2118). Annual population data at the municipal level was provided by the National Institute of Statistics and Economic Studies (INSEE) in France and the Statistical Institute of Catalonia (Idescat) in Spain. Linear regression was used to extrapolate municipal population data for 2015 in France, due to delayed reporting.

Several parameters were excluded because data from a substantial proportion of days were missing, including manually measured water quality indicators (e.g., heterotrophic plate counts in finished water at location 1, free chlorine in the distribution system at location 5), and raw water turbidity and daily flow of finished water at location 3. For higher resolution datasets (e.g., sensor readings taken multiple times per day), daily (locations 1 and 3) or monthly (location 5) averages were generated. Daily or monthly minima were extracted for free chlorine, and daily or monthly maxima for turbidity, to capture suspected high-risk conditions. Values below lower detection limits were set to zero, and values above upper detection limits were set to the upper detection limit. Missing data were left as missing. In particular, values for air temperature and precipitation were not reported from February 21–28 of each year for location 1 only. If extreme values were observed, these were submitted to the utility for reexamination, although in general, outliers were deemed to be correct and were not excluded from the dataset.

2.3. Data analysis

A new continuous variable was created for daily runoff at locations 1 and 3, defined as the amount of precipitation over 10 mm at temperatures above 0 °C (Beaudeau et al., 2014a). New dummy variables were created to flag "heavy" precipitation events above the 90th percentile (5.2 mm for location 1; 8 mm for location 3) over the multiyear study period (Carlton et al., 2014; Curriero et al., 2001), "flush" events defined as runoff following a two-week antecedent dry period (Tiefenthaler and Schiff, 2003; Yuan et al., 2017), and day-to-day rises in average turbidity greater than the interquartile range (0.129 NTU at location 3) (Barbeau et al., 2003). Control parameters included the full date time series (to account for multiyear trends), month of the year (to account for seasonal pathogen transmission trends), day of the week (to account for weekends), work/school holidays (to account for medical visit behaviors), day of the month (to account for pay period effects), and one-week or one-month lag of cases (to account for residual auto-correlation from secondary contagion).

Data analysis was conducted using SAS 9.4. Parameters were plotted over time to visualize trends, and descriptive statistics were calculated. Correlation tests identified multicollinearity among variables, as well as variables highly correlated with the outcome measure. For daily data from locations 1 and 3, univariable Poisson regression models were run to test lag times of up to 15 days for each exposure variable based on existing studies (Beaudeau et al., 2014b, 2012; De Roos et al., 2017). For monthly data from location 5, a one-month lag time was considered, incorporating about 30–60 days prior to case reporting (depending on when the case occurred within the month). The most appropriate time lag(s) were identified for each parameter, taking into account expected transit time, pathogen latency, reporting delays, consistent direction of effect, and statistical significance over multiple days. Moving averages (or moving totals for dummy variables) were calculated for multi-day time windows where appropriate.

Generalized additive models with Poisson regression (Beaudeau, 2003) were used to assess the relationship between control and exposure parameters and recorded acute gastroenteritis cases, using cubic smoothing splines, a natural log link function, and an offset equal to the annual population from the municipalities in the water service area. The GAM procedure was applied in SAS, constraining the parameter estimate for the offset to one, which is equivalent to modeling the rate as the dependent variable (Eq. (1)). The procedure relaxes the assumption of linearity by separating linear terms (traditional multiple regression output) and non-linear splines, which are additive. Thus, splines are a discretionary addition to the linear terms for continuous variables only.

$$\ln(\text{Cases/Population}) = \beta_0 + \beta_i*\text{Controls} + \text{spline(Controls)} + \beta_j*\text{Exposures} + \text{spline(Exposures)} \quad (1)$$

Models were fit separately to the full datasets at each location based on correlation tests, the univariable model results, parameter significance after introduction of controls, and plausibility based on existing literature regarding exposure pathways. Potential interaction and higher order terms were considered, and two alternative models were fit by dropping non-significant or multicollinear terms. The final model for each location was selected to minimize overall deviance. Splines were included by default for continuous exposure variables, and retained especially when significant nonlinearity was identified. Generalized cross-validation was used at first to select optimal degrees of freedom for the splines; however, extremely high or low values were then restricted to a range of 4 (default) to 12 degrees of freedom. Temporal indicators (WSP implementation status, month, weekday, work/school holidays, day of month) were entered as class (categorical) variables, along with the lagged number of cases as a continuous variable and a spline function of date (converted to a continuous numeric sequence), to better isolate which variations in the data stemmed from these suspected influences.

All-ages and all-municipalities health data were used to maximize power of the model, since the previous study showed trends were driven by the largest (adult) group and the full water service area at location 3 (Setty et al., 2017).The datasets were not split into training and validation datasets, since this would further reduce power and the models were not intended for prediction. Where adequate sample size allowed, the stage of WSP implementation was tested as an effect modifier by stratifying the datasets into relevant time periods (before WSP team formation vs. after WSP certification) to determine how the relationship between the most relevant exposure variables and acute gastroenteritis outcomes may have differed within subsets of the data.

2.4. Sensitivity testing

Sensitivity analyses were conducted to evaluate the influence of key methodological decisions (Bhaskaran et al., 2013). One such option was to exclude turbidity and free chlorine data suspected of being affected by temporary plant shutdowns or sensor failures at location 3, although no consistent historical records were available to accurately document these events. A suspected shutdown or failure was defined as a free chlorine value

less than 0.05 mg/L for more than two hours, or an unchanged turbidity value for at least 24 h. Sensor data from location 1 were not available (Table 3) and sensor data from location 5 were validated by technicians in the plant at the time of recording. Additional sensitivity tests were conducted on the location 1 model for the choice of antecedent dry period (using 12 or 16 days rather than 14) and the time lag of cases selected to control for secondary contagion (using 3, 5, or 9 days rather than 7). Time lags up to 45 days (rather than 15) were also examined for the most relevant exposure variables at locations 1 and 3.

3. Results

Descriptive statistics were calculated for the range of parameters (Table 4). Recorded acute gastroenteritis cases and rates were much higher at the French locations due to differences in surveillance methods. Air temperatures represent daily averages in France and daily maxima in Spain (Table 3). The maximum amount of missing data was 2.3% for weather records at location 1. For sensitivity analyses, cleaning of online sensor datasets to remove periods of suspected plant shutdowns and sensor failures at location 3 resulted in a further loss of about 6% of the turbidity data and about 4% of the free chlorine data. At location 3, free chlorine daily averages and daily minima showed very little variation, while raw water turbidity and river flow at location 5 varied widely.

When all-causes acute gastroenteritis rates were graphed over time, seasonal winter peaks were apparent in France (locations 1 and 3), likely due to person-to-person norovirus transmission (Figs. 1 and 2). Both French locations revealed some tapering off of seasonal peaks in later years of the dataset. Rates at location 5, in contrast, appear to increase over time (Fig. 3). Seasonal patterns are less apparent, potentially due to the different public health surveillance methods (lower resolution monthly hospital cases in Spain versus higher resolution daily prescription monitoring in France) and/or the milder climate in Spain (higher and less variable temperature range).

Where daily data were available, univariable testing of lag times up to 15 days prior to case reporting showed some significant single-lag relationships for all examined variables prior to introduction of control variables, using the adaptive Holm procedure for p-value adjustment (Table 5). In comparison to location 3, stronger multiday relationships between hydrological parameters (related to precipitation, runoff, and flow) and acute gastroenteritis were seen at location 1, where the surface water supply is directly influenced by weather events and alternate water sources are not used. Depending on the variable, lag times may include transit time prior to exposure (e.g., to plant intake, through treatment plant, and/or through distribution system). With similar transit times at locations 1 and 3, hydrological exposure variables were most consistently significant 6–9 days prior to case reporting, although some multiday windows of significance were also seen with variables recorded between 1-3 days and 13-15 days prior to case reporting. For some variables, transformation better captured suspected exposure pathways and improved relevance to overall health outcomes. For example, at location 3 the turbidity daily maxima and interquartile "rise" in daily average turbidity variables performed better than the turbidity daily average.

After introduction of controls, fewer exposure variables remained significant in the final models,[1] which were selected based on goodness

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[1] $f(\text{controls})_{\text{locations } 1,3} = \beta_0 + \beta_{1\text{-}5}*\text{Year} + \beta_{6\text{-}17}*\text{Month} + \beta_{18\text{-}48}*\text{Day of Month} + \beta_{49\text{-}55}*\text{Weekday} + \beta_{56\text{-}57}*\text{Work Holidays} + \beta_{58\text{-}59}*\text{School Holidays} + \beta_{60}*\text{Lagged Cases}_7 + \beta_{61}*\text{Date} + \text{spline(Date)}$

$f(\text{exposures})_{\text{location } 1} = \beta_{62}*\text{Flush Event}_{6\text{-}8} + \beta_{63}*\text{Precipitation}_{\text{Average},6\text{-}8} + \text{spline}(\text{Precipitation}_{\text{Average},6\text{-}8})$

$f(\text{exposures})_{\text{location } 3} = \beta_{62}*\text{Temperature}_1 + \text{spline}(\text{Temperature}_1) + \beta_{63}*\text{Turbidity Max}_{0\text{-}15} + \text{spline}(\text{Turbidity Max}_{0\text{-}15})$

$f(\text{controls})_{\text{location } 5} = \beta_0 + \beta_{1\text{-}10}*\text{Year} + \beta_{11\text{-}22}*\text{Month} + \beta_{23}*\text{Lagged Cases}_1 + \text{spline}(\text{Lagged Cases}_1) + \beta_{24}*\text{Date} + \text{spline(Date)}$

$f(\text{exposures})_{\text{location } 5} = \beta_{25}*\text{Temperature}_1 + \text{spline}(\text{Temperature}_1) + \beta_{26}*\text{Temperature}_1{}^2 + \text{spline}(\text{Temperature}_1{}^2) + \beta_{27}*\text{Precipitation}_1 + \text{spline}(\text{Precipitation}_1) + \beta_{28}*\text{Turbidity}_{\text{Fin.},1} + \text{spline}(\text{Turbidity}_{\text{Fin.},1}) + \beta_{29}*\text{Free Cl}_{\text{Fin.}} + \text{spline}(\text{Free Cl}_{\text{Fin.}}) + \beta_{30}*\text{Flow}_{\text{Fin.}} + \text{spline}(\text{Flow}_{\text{Fin.}})$

Table 4
Descriptive statistics for continuous and count variables considered for inclusion in the models at each location.

Location 1 (recorded or computed daily values)

Variable	Units	# Days	% Missing	% Non-Zero	Min	Median	Mean	Max	Variance
Cases	/day	2130	0%	96.6%	0	12	12.7	55	78.5
Rate	cases/ 1000 person-days	2130	0%	96.6%	0	0.252	0.273	1.20	0.036
Air Temp	°C	2081	2.3%[a]	> 99.9%	−8.1	12.8	12.4	29.5	43.7
Precipitation	mm	2081	2.3%[a]	42.3%	0	0	1.7	50.0	17.1
River Flow	m³/s	2129	< 0.1%	100%	46.7	152.0	221.9	865.0	$2.71E^4$

Location 3 (recorded or computed daily values)

Variable	Units	# Days	% Missing	% Non-Zero	Min	Median	Mean	Max	Variance
Cases	/day	1967	0%	97.9%	0	12	14.3	123	140.9
Rate	cases/ 1000 person-days	1967	0%	97.9%	0	0.281	0.335	2.96	0.078
Air Temp	°C	1953	0.7%	100%	−5.4	14.8	14.5	30.6	39.5
Precipitation	mm	1953	0.7%	40.1%	0	0	2.2	49.6	25.8
Turbidity (Fin. Water)	NTU	1960	0.4%	99.7%	0	0.23	0.33	9.92	0.29
Turbid Max (Fin. Water)	NTU	1960	0.4%	99.7%	0	0.34	0.79	10.02	2.75
Free Cl (Fin. Water)	mg/L	1961	0.3%	96.7%	0	0.12	0.13	0.61	$3.7E^{-3}$
Free Cl Min (Fin. Water)	mg/L	1961	0.3%	87.4%	0	0.08	0.08	0.52	$2.5E^{-3}$

Location 5 (recorded or computed monthly values)

Variable	Units	# Mos	% Missing	% Non-Zero	Min	Median	Mean	Max	Variance
Cases	/month	132	0%	99.2%	0	4	4.8	15	7.1
Rate	cases/ 1000 person-days	132	0%	99.2%	0	0.028	0.033	0.101	$3.28E^{-4}$
Air Temp	°C	132	0%	100%	11.0	21.7	21.9	34.3	36.0
Precipitation	mm	132	0%	99.2%	0	30.4	45.0	223.6	1961.4
Water Temp	°C	132	0%	100%	7.32	17.90	17.37	28.03	40.26
Turbidity (Raw Water)	NTU	132	0%	100%	4.64	120.70	215.67	943.64	$5.23E^4$
Turbid Max (Raw Water)	NTU	132	0%	100%	13.00	2300	4871	39000	$4.48E^7$
UV Abs. (Raw Water)	/100 cm	132	0%	100%	6.59	10.91	11.59	20.28	7.49
Turbidity (Fin. Water)	NTU	132	0%	100%	< 0.01	0.17	0.17	1.03	0.01
Turbid Max (Fin. Water)	NTU	132	0%	100%	0.17	0.64	8.91	540	4058
TOC (Fin. Water)	mg/L	131	0.8%	100%	0.38	1.30	1.56	4.13	0.63
Free Cl (Fin. Water)	mg/L	132	0%	100%	0.69	0.96	0.96	1.24	0.01
Free Cl Min (Fin. Water)	mg/L	132	0%	68.2%	0	0.21	0.24	0.64	0.04
Flow (Fin. Water)	x 10³ m³/day	132	0%	100%	113.9	280.4	313.6	2318.9	$4.52E^4$
% Surface vs. Groundwater	%	132	0%	100%	< 1	76	73	97	4

[a] Values for air temperature and precipitation were missing from February 21–28 of each year at location 1.
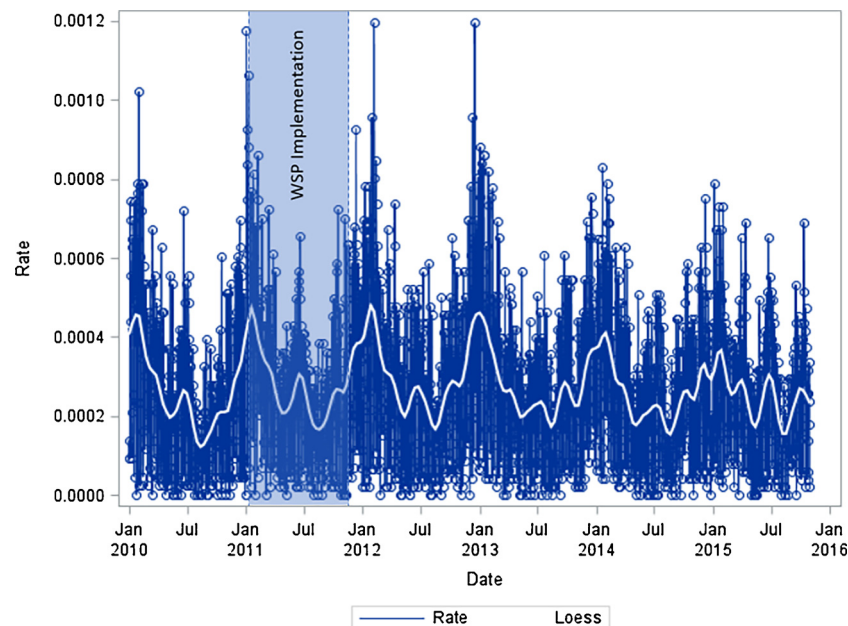
Fig. 1. Daily acute gastroenteritis incidence rates (cases/day) comprising all exposure pathways at location 1.
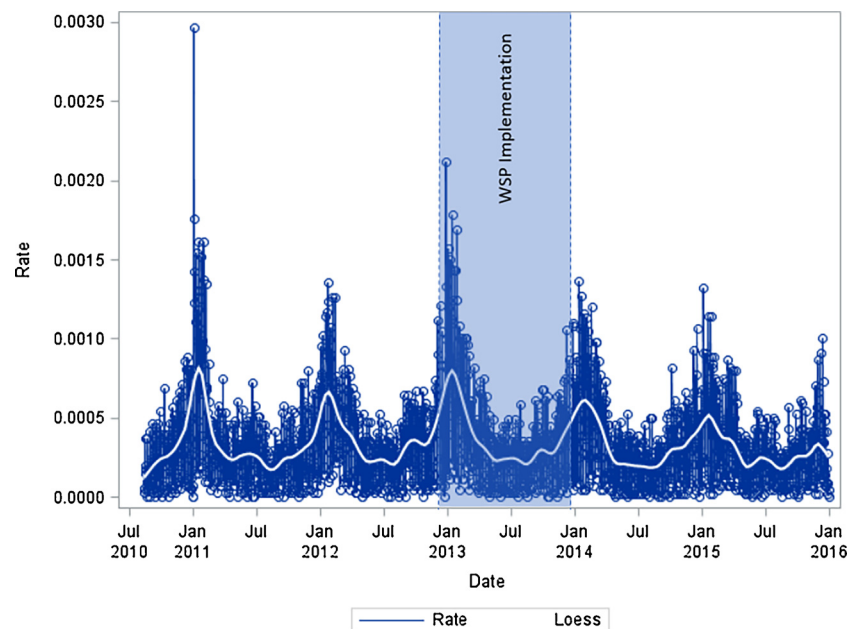
Fig. 2. Daily acute gastroenteritis incidence rates (cases/day) comprising all exposure pathways at location 3.
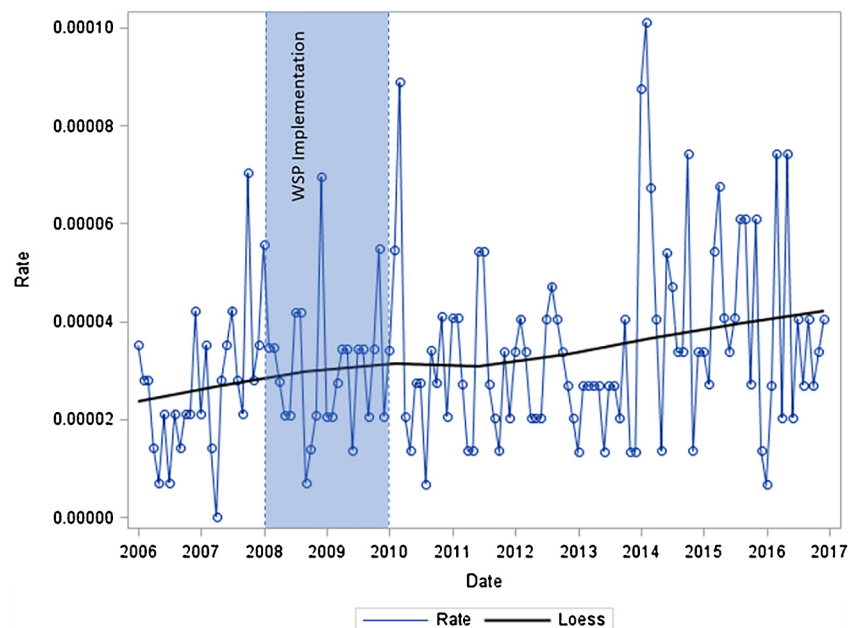

Fig. 3. Monthly acute gastroenteritis incidence rates (cases/month) comprising all exposure pathways at location 5.

of fit. Model diagnostics suggested the Poisson link was appropriate for the data, as Pearson's scaling factor was less than two in all cases. Model deviances were similar to the expected values based on the number of observations and degrees of freedom. As expected, parameter estimates were fairly small (Table 6), since drinking water exposures are likely secondary to other transmission methods in high-income settings. The time lags and moving averages tested were generally held constant for each variable added to the model where they were based on co-occurring events (i.e., days 6–8 for location 1; days 6–9 for location 3 hydrological variables, days 6-8 and 13-14 for location 3 water quality variables). If independent variables were highly correlated (e.g., precipitation vs. runoff), the one with the stronger association was retained. Some moderately correlated explanatory variables (e.g., 6–8 day lagged precipitation and flush events at location 1) were retained due to suspected direct and indirect effects. The rate

ratio compares exposed to unexposed persons, with a null value of one. Percentage change was calculated by dividing the difference between the rate ratio and the null value by the rate ratio, estimating the change in disease burden associated with a one-unit or one-level change in exposure.

Among exposure variables, higher air temperatures were significantly associated with fewer cases of acute gastroenteritis at locations 3 and 5 (Table 6). There was some evidence to support a higher-order relationship, suggesting a small number of additional cases at very high temperatures (e.g., location 5 air temperature squared, $\beta = 0.005$, $p = 0.052$). Some risk was associated with hydrological factors, especially flush events for the surface water source at location 1. Flush events could not be tested at location 5 due to the monthly data resolution. Precipitation showed a positive association at location 5, despite the management intervention of switching to groundwater

Table 5
Significance of linear parameter estimates regressing acute gastroenteritis rates on individual exposure variables over tested lag times (in days prior to case reporting) prior to introduction of control variables at locations 1 and 3 (p < 0.1*, p < 0.01**, p < 0.001*** with adaptive Holm adjustment). If significant, shading indicates a positive linear association. For continuous variables, bold indicates significant nonlinearity. Boxes show variables and associated lag times included in final models after introduction of controls.

Variable[1]	Lag (in days)														
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Location 1															
Air Temperature	***			***					*	*	***	*		**	
Precipitation	*	**	*	**	**	***	***	***	**		**	*	***		*
Runoff				*	***	***	***			***		*	***		
Heavy Precip.		***		*		**	***	**	***				*		*
Flush Event	***					***	***	***					***	***	***
River Flow		*					**								
Location 3															
Air Temperature	***						*	**				*	**		**
Precip		***	*			***	***	***	***				***		
Runoff						***		***	***	*	*		**		
Heavy Precip.		***	***			**		***	***	***			**	*	
Flush Event	*	***	***			***			***	*			***	**	
Turbid. Daily Ave.			***		***						***				*
Turbid. Daily Max	***		***	*		***	***	***	**	**	***	*	***	***	**
Rise in Turbidity		*	***	***		***	***	***		***			***	***	***
Free Cl Daily Ave.			*							**				*	***
Free Cl Daily Min	***	***	***	**	***	***	***		***			***	***	***	***

[1]Model form for testing univariable lag times: ln(Cases/Population) = β0 + β1*Exposure + … + β15*Exposure + spline1(Exposure) + … + spline15(Exposure).

Table 6
All-ages acute gastroenteritis incidence rate ratios for the linear component of only significant exposure variables (at specified lag times prior to case reporting) from the final model at each location.

Location	Parameter	Parameter Estimate	P-Value	Rate Ratio (RR)	RR 95% Confidence Interval	Percent Change (RR-1)/RR	Significantly Nonlinear?
1	Flush (days 6-8)	0.109	0.003	1.115	1.035, 1.200	10.3%	N/A
	Precipitation (days 6-8)	−0.011	< 0.001	0.989	0.983, 0.996	−1.6%	No
3	Air Temp (day 1)	−0.009	< 0.001	0.991	0.987, 0.994	−0.9%	Yes
	Turbid Max (days 0-15)	0.042	< 0.001	1.043	1.024, 1.061	4.3%	Yes
5	Air Temp (month 1)	−0.264	0.029	0.768	0.608, 0.969	−30.3%	No
	Precipitation (month 1)	0.025[a]	0.043	1.025	1.001, 1.050	2.5%	No
	Flow Fin.	0.009[a]	0.002	1.009	1.003, 1.014	0.9%	No
	Turbid Fin. (month 1)	0.101[a]	0.025	1.106	1.014, 1.206	9.6%	No
	Free Cl	−0.177[a]	0.011	0.837	0.733, 0.956	−19.4%	No

[a] For interpretation, estimates are scaled from a one-unit change to a 0.1-unit change for finished water average turbidity (NTU) and free chlorine (mg/L) at location 5. Estimates are scaled from a 1-unit change to a 10-unit change for precipitation (mm) and finished water flow (x 10^3 m^3/day) at location 5.

sources during heavy rain. Precipitation was negatively associated with acute gastroenteritis at location 1, potentially due to dilution, improved coagulation effectiveness, or the ultrafiltration step added in July 2010. At location 1, the trended spline for the 6–8-day lagged precipitation moving average showed a non-significant deviation from the linear trend between 5 and 15 mm, which coincided with the 10-mm value used to define runoff and flush events (Fig. 4). In the monthly time series model at location 5, no effects were significantly nonlinear. Examples of significant nonlinear trends are presented for the prior day's air temperature and daily maximum turbidity moving average from location 3 (Figs. 5 and 6).

At locations 1 and 3, control variables included in the final models (not shown in Table 6) were related to acute gastroenteritis reporting, including year and month (p < 0.10 for each). Day of the month was significant (p < 0.01 on most days) at location 3, with greater reporting at the beginning of the month. At location 1, reporting appeared more common toward the end of the month (p < 0.20 on most days). At both locations, weekday had a significant influence on reporting of acute gastroenteritis (p < 0.001 for each day), with an overall decreasing trend from Monday to Sunday. Reporting was significantly lower on work and school holidays (p < 0.001 for each), likely due to changes in care-seeking behaviors and reduced access to pharmacies.
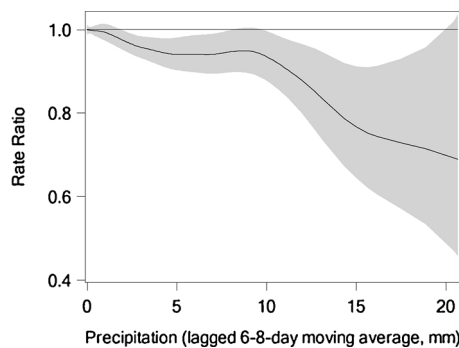
Fig. 4. Trended nonlinear relationship between 6–8-day precipitation moving average and acute gastroenteritis rate ratio at location 1, with 95% confidence band (spline χ^2 = 4.82, p = 0.443).
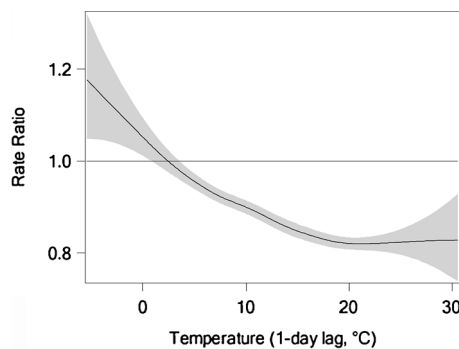

Fig. 5. Trended nonlinear relationship between the one-day lag of air temperature and acute gastroenteritis rate ratio at location 3, with 95% confidence band (spline χ^2 = 10.83, p = 0.013).
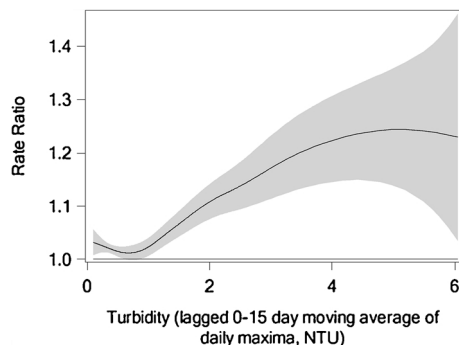

Fig. 6. Trended nonlinear relationship between the 0–15 day moving average of daily maximum turbidity in finished water and acute gastroenteritis rate ratio at location 3, with 95% confidence band (spline χ^2 = 10.53, p = 0.015).

The seven-day lag of cases was significant at location 1 (β = 0.005, p < 0.001) and location 3 (β = 0.007, p < 0.001). In contrast, at location 5, seasonal control variables (year, month, and school holidays), as well as the one-month lag of cases, were not significantly related to the monthly acute gastroenteritis records.

The final models were then applied to data stratified by WSP implementation status (Table 7). At location 1, the flush parameter had a robust association (β = 0.148, p = 0.046) in the before period (365 days), whereas the 6–8-day precipitation moving average parameter was not significant (β = −0.002, p = 0.799). In the after period (1420 days), the flush parameter remained significant (β = 0.099, p = 0.033), and the precipitation parameter also became significant (β = −0.012, p = 0.002), potentially due to treatment improvements (e.g., ultra-filtration). When data were subdivided by WSP status at location 3, the turbidity indicator had a similar parameter estimate (β = 0.042,

p = 0.087) before WSP implementation (823 days), but was not highly significant. The relationship between turbidity and health outcomes appeared to weaken substantially (β = −0.008, p = 0.669) in the period after WSP implementation (741 days). At location 5, the before period (24 months) had too few observations to model. In the after period (84 months), the most relevant indicators were the one-month lag of average precipitation (β = 0.005, p = 0.011), finished flow (scaled β = 0.010, p = 0.002), and the one-month lag of average turbidity (scaled β = 0.113, p = 0.103). The precipitation variable showed significant nonlinearity in the after period (spline χ^2 = 5.75, p = 0.039) with risk peaking at more than 70 mm per month.

3.1. Sensitivity testing

When examining sensitivity to suspected plant shutdowns and sensor failures, the full dataset seemed to offer a better approximation of the exposures of interest. Including all turbidity data improved significance of the exposure variable but increased model deviance. Using the cleaned dataset for location 3, the turbidity variable of interest (15-day moving average of daily maxima with 6% missing data) was not significant (p = 0.120). More influence shifted instead to the control variables, while decreasing model deviance. The cleaned chlorine data set was not ultimately used; this variable was excluded from the final model due to suspected multicollinearity with turbidity.

Sensitivity tests altering the antecedent dry period at location 1 resulted in a non-significant flush indicator (β = 0.044, p = 0.221 at 12 days and 0.075, p = 0.052 at 16 days), suggesting the model was sensitive to this value and the literature-based estimate of 14 days was appropriate for this location. The model was robust to shorter lag times for cases (3 or 5 days) used to control for secondary contagion, but not to longer lag times (β = 4.98E^{-4}, p = 0.654 for 9 days). Testing longer time lags for the flush parameter (up to 45 days) suggested two additional periods of multi-day significance (> 2 days) at 20–22 days and 28–30 days (p < 0.001). Since the spacing of these windows was relatively even in the univariable models, the later periods may reflect cycles of secondary contagion that dissipate over time. Later time periods (beyond 6–8 days) were not significant when introduced into the final location 1 model with controls. The turbidity maxima at location 3 similarly showed two additional periods of multi-day significance at 20–22 days and 27–29 days (p < 0.001), which were significant (β = 0.026, p < 0.001 and β = 0.027, p < 0.001, respectively) when introduced into the final location 3 model, alongside controls.

4. Discussion

Importantly, this study identified a number of significant linkages between drinking water-related exposures and health outcomes at all studied WSP locations. This served to clarify the mechanism for the large-scale changes in health outcomes noted in an earlier study, and validate that the observed changes may have stemmed from drinking water safety interventions (Setty et al., 2017). The most important explanatory variables for acute gastroenteritis outcomes were flush events tied to surface runoff after an antecedent dry period at location 1, and finished water daily average or maximum turbidity levels across locations with groundwater or combined surface and groundwater sources (Table 6). Site-specific modeling exercises are recommended, as data availability and relevant processes (e.g., source water types, treatment approaches, cultural factors) varied among locations.

Despite concerns about low-resolution public health surveillance data in Spain, location 5 yielded the longest-running eleven-year dataset and the model benefited from matching the health data with high-resolution water quality data (i.e., central tendencies calculated from hundreds to thousands of measurements per month). Models revealed a number of significant explanatory variables, albeit with slightly less statistical confidence (Table 6), demonstrating the potential value of

Table 7

All-ages acute gastroenteritis incidence rate ratios for the linear component of relevant variables (at specified lag times prior to case reporting) tested after stratification of data into time periods before and after WSP implementation at each location.

Location	WSP Status	Parameter	Parameter Estimate	P-Value ($^*p < 0.05$)	Rate Ratio (RR)	RR 95% Confidence Interval	Percent Change (RR-1)/RR	Significantly Nonlinear?
1	Before (n = 365)	Flush (days 6-8)	0.148	0.046*	1.160	1.000, 1.345	16.0%	N/A
	Before (n = 365)	Precipitation (days 6-8)	−0.002	0.799	0.998	0.981, 1.015	−0.2%	No
	After (n = 1420)	Flush (days 6-8)	0.099	0.033*	1.104	1.006, 1.212	10.4%	N/A
	After (n = 1420)	Precipitation (days 6-8)	−0.012	0.002*	0.988	0.980, 0.996	−1.2%	Yes
3	Before (n = 823)	Turbid Max (days 0-15)	0.042	0.087	1.043	0.993, 1.094	4.3%	Yes
	After (n = 741)	Turbid Max (days 0-15)	−0.008	0.669	0.992	0.954, 1.031	−0.8%	No
5	Before (n = 24)	*Too few observations to model*						
	After (n = 84)	Precipitation (month 1)	0.047[a]	0.011*	1.048	1.011, 1.086	4.8%	Yes
	After (n = 84)	Flow Fin.	0.010[a]	0.002*	1.010	1.004, 1.016	1.0%	No
	After (n = 84)	Turbid Fin. (month 1)	0.113[a]	0.103	1.119	0.978, 1.281	11.9%	No

[a] For interpretation, estimates are scaled from a one-unit change to a 0.1-unit change for finished water average turbidity (NTU) at location 5. Estimates are scaled from a 1-unit change to a 10-unit change for precipitation (mm) and finished water flow (x 10^3 m^3/day) at location 5.

time series models over a range of time scales (Bhaskaran et al., 2013). Hospital records of acute gastroenteritis may be common in public health surveillance data in other high-income nations, making location 5 a potentially useful and transferable case example for risk assessment.

4.1. Level of risk

Based on raw 2010–2015 data from the French locations, daily recorded rates of acute gastroenteritis ranged from zero to 2.96 cases per 1000 person-days (Table 4) or 0.09–0.14 cases per person per year on average. Recorded rates were much lower in Spain due to differences in the public health surveillance method. Estimating the drinking water attributable burden at around 12% (Colford et al., 2006) would put attributable rates for these areas at approximately 0.011–0.017 cases per person-year. These rates are fairly low (Messner et al., 2006; Murphy et al., 2016) but relevant in comparison acceptable disease risks of $1E^{-3}$ cases per person-year (WHO target) or $1E^{-4}$ cases per person-year (the Suez company's internal target). What might be considered acceptable by the populations under study is subjective (Hunter and Fewtrell et al., 2001). At location 3, for example, a previous study (Setty et al., 2017) noted that cancer mortality risk from disinfection byproducts (Corso et al., 2017) poses a concern alongside acute gastroenteritis morbidity. Therefore, there may be a need to optimize multiple public health goals when managing drinking water supplies. Accounting in a common unit such as disability-adjusted life years could assist with transparent decision making and communication in such cases (WHO, 2010).

4.2. Weather

Air and water temperature may have multiple effects on acute gastroenteritis occurring on different timescales and via different routes. These include effects of dehydration on reporting in the near-term (Beaudeau et al., 2014a) and longer-term effects on pathogen survival in the environment and on surfaces, as well as bacterial multiplication in food (Zhou et al., 2013). The nonlinear trend for the one-day lag of temperature at location 3 (Fig. 5), for example, demonstrates the protective role of increasing temperatures in a low temperature range (potentially from less time spent indoors) and the harmful role of increasing temperatures at higher ranges (potentially from symptom worsening due to dehydration). The prior month's air temperatures were strongly associated with disease rates at location 5 (Table 6), where seasonality is less distinct (Fig. 3). The relationship between finished flow and acute gastroenteritis at location 5 (Table 6) was not significantly nonlinear (spline p = 0.146), but graphically the risk

heightened at production of about 650,000 m^3/day (roughly double the average flow), potentially due to increased drinking water consumption during periods of high demand.

Flush events accompanied by nonpoint source pollution and/or sediment resuspension were significantly related to health outcomes (Table 6) and appeared to play a role in pathogen transport at location 1; however, health risks were also negatively associated with increasing precipitation, potentially via dilution or an improved coagulation or ultrafiltration treatment step in more turbid source waters. Taken in combination, a flush event could correspond to a greater than null risk level in the range from about 3.5 mm (sufficient to define a single flush event on one of the preceding 6–8 days) to 12 mm (where risk begins to decline sharply) of average precipitation during the preceding 6–8 days (Fig. 4; Table 6). The relative reduction in health risks previously observed at location 1 (Setty et al., 2017) and the stratified time period models from this study (Table 7) suggest management measures associated with the WSP have been effective in this location. Continuous water quality data and operational records that might offer greater insight were not available due to temporary reassignment of the plant manager from 2011 to 2013.

4.3. Multiyear trends

The multiyear nonlinear trend in acute gastroenteritis rates associated with the date series at location 1 suggested an initial steep decline (from 2010) followed by settling around the null value and finally a slight upswing in 2015 (p < 0.001). This matches broader trends identified since 2009 for all of France using prescription algorithm data (Rivière et al., 2017). The nonlinear trend at location 3 showed relatively even fluctuations around the null value, with peaks in 2011, 2013, and 2015 and dips in 2012 and 2014 (p < 0.001). The location 5 date series was not significantly nonlinear, but rates appeared to increase from 2006 to 2008 and then dropped to a smaller degree in 2014 (p = 0.166). This coincides with the trend observed nearby in France based on practitioner reporting prior to 2009, via the GP Sentinelles network (Rivière et al., 2017).

Multiyear differences may be due to long-term random variation in climate patterns and/or changes in pathogen virulence, which is suspected in France (Rivière et al., 2017). Nevertheless, acute gastroenteritis rates at location 1 were previously shown to have been significantly lower following WSP implementation relative to a nearby non-WSP comparison area, potentially due to treatment plant upgrades (Setty et al., 2017). Few significant changes were observed in finished water quality, suggesting that source water quality and watershed activities remained fairly stable; however, compliance with turbidity and

total coliform standards improved, matching the identified health outcomes. Based on the present study, the comparison area downstream of the urban center may also have been more vulnerable to nonpoint source pollution from impermeable surfaces during flush events. Both areas were upstream of (not affected by) the urban area's largest combined sewer overflow (Even et al., 2007; Passerat et al., 2010).

4.4. Turbidity

Modeling results suggested turbidity-associated risk was driven by intermittent peaks, rather than steady state conditions. Turbidity levels above 1 NTU often relate to pathogen exposure, although variation may stem from site heterogeneity (Beaudeau, 2003; De Roos et al., 2017). Current French and Spanish standards recommend maintaining turbidity levels below 0.5 NTU at the plant outlet (Setty et al., 2017). Turbidity levels at location 3 included intermittent peaks ranging from 0–6 NTU (Table 4), supporting the finding of a 4.2% increase in disease burden associated with each 1-NTU rise in the lagged 0-15-day moving average of daily turbidity maxima (Table 6). The trended rate ratio rose steadily between 1 and 5 NTU (Fig. 6). In an alternative model segregating turbidity by shorter lag windows, 6–8-day and 13-14-day lags were significant ($\beta = 0.019$, $p < 0.001$ and $\beta = 0.020$, $p < 0.001$, respectively); however, overall model deviance was reduced by including the longer time period. Sensitivity tests showed relevance of this variable over up to a 30-day period in evenly spaced windows. Because transit time was fairly consistent throughout the distribution system, this suggests either a higher rate of secondary contagion (compared to location 1) or possibly the relevance of more than one pathogen type and corresponding incubation period at location 3. At location 5, the averaged one-month lag of finished water turbidity values had a range of about 0–1 NTU and the final model suggested a 9.6% increase in acute gastroenteritis rates for every 0.1 NTU increase in the monthly average. Observed changes in the monthly average were influenced in some cases by up to three peaks per month over 2 NTU.

4.5. WSP implementation status

The role of WSP implementation differed among locations. The before period at location 5 could not be modeled due to data paucity. Still, the increase in acute gastroenteritis rates previously noted among adults (Setty et al., 2017) combined with the significant associations between drinking water related exposures and health outcomes found in this study recommend additional attention to risks such as precipitation events and turbidity peaks. At location 1, a protective association between heavier precipitation and health outcomes appeared following WSP implementation, suggesting treatment improvements (e.g., ultrafiltration installation in 2010 or variable coagulant dosing) have been effective. When time periods were examined individually at location 3, the relationship between turbidity and acute gastroenteritis appears to have weakened in the post-WSP period, perhaps due to the role played by more consistent lower limits for chlorine. In a previous study (Setty et al., 2017), though, this did not correspond to a reduced incidence of acute gastroenteritis. Despite improved compliance with the chlorination lower limits (established during WSP implementation in 2012), average free chlorine increased only slightly (0.015 mg/L) and other water quality indicators (total coliform, heterotrophic plate count, turbidity) worsened in the post-WSP period (Setty et al., 2017).

The WSP controls limit free chlorine to a narrow range of values, and this low variance (Table 4) as well as apparent multicollinearity with turbidity made it difficult to characterize the free chlorine parameter in the final model (Table 6). Interim modeling results suggested increased free chlorine was harmful at location 3, although ongoing testing of one chlorine-resistant pathogen (*Cryptosporidium*) yields consistently negative results. Prior to treatment process changes in 2011 (adding a pre-chlorination/pre-oxidation step and UV), highly turbid water was discarded. Retaining highly turbid water may account

for the apparent worsening in water quality. Alternatively, chlorination could mask cultivable fecal indicators (e.g., *E. coli*), offering a false sense of assurance if the indicator organisms are more susceptible to disinfection than pathogens of potential concern (e.g., norovirus) (Petterson and Stenström, 2015). Pre-oxidation has also been accomplished using chlorine gas (Cl_2) rather than chlorine dioxide (ClO_2) since 2012, which could differentially affect pathogen survival. Controlling periodic chlorine spikes could have affected pathogen survival in treated water or distribution pipe biofilms. Or, if automated chlorine dosing is variable, we may have observed a strong positive association due to increased dosing when water is of poorer quality. Given suspected synergies between the free chlorine and turbidity variables, new WSP controls and/or treatment barriers for turbidity may be warranted as the WSP is iteratively updated.

4.6. Comparison with other studies

This study largely confirms the literature on drinking water-related gastrointestinal disease and contributors to health risks (Chhetri et al., 2017; Levy et al., 2016), while eliciting potential areas of site-specific management intervention. Precipitation, generally thought to be harmful, was inconsistently associated with acute gastroenteritis rates among sites, potentially due to differences in treatment processes and pollution sources. Chlorination, generally thought to be protective, also played an inconsistent role among sites. Relaxing the linearity assumption via generalized additive modeling offered a more nuanced understanding of variability in the relationship between acute gastroenteritis rates and common exposure variables. Transformation of variables to describe more precise exposure mechanisms (e.g., flush events considering the antecedent dry period as opposed to daily precipitation alone) was valuable in developing site-specific understanding of risks.

Our study implicated periodic turbidity peaks and nonpoint source pollution of surface waters as key components of risk, although data was lacking at various points along the chain between water contamination, treatment, delivery, consumption, symptom development, and disease reporting. In a previous study (Setty et al., 2017), distribution systems appeared to play a lesser role than treatment processes at these locations; however, the magnitude of distribution networks' relative contribution to contamination is understudied (Colford et al., 2006). In a recent review of waterborne outbreaks in Europe, North America, and New Zealand (Moreira and Bondelind, 2017), contaminants were introduced into distribution networks by cross-connections, pipe breaks, and wastewater intrusion. Consumers with predominantly surface water sources, such as locations 1 and 5, were most vulnerable to outbreaks stemming from risks such as wastewater discharge, increased turbidity and color, and disinfection equipment malfunction. Primary causes of groundwater contamination were intrusion of animal feces or wastewater during heavy rain (Moreira and Bondelind, 2017).

Information about pathogens of concern would help utility operators to manage risks. The 6–9 day lag times observed for hydrological variables in France (inclusive of transit time, treatment, distribution, exposure, incubation, and reporting) generally conformed with other studies (De Roos et al., 2017). These lag times suggest viral disease agents, which, among waterborne pathogens, have the shortest incubation period and are the most common cause of acute gastroenteritis in high income settings (De Roos et al., 2017; Rivière et al., 2017). Pathogens connected with waterborne outbreaks in other high-income countries include norovirus, rotavirus, *Campylobacter, Cryptosporidium*, and *Giardia* (Moreira and Bondelind, 2017). In France, viral agents likely include norovirus along with rotavirus, astrovirus, adenovirus, and sapovirus (Lopman et al., 2003). Within-month chlorine levels had a protective association with health risk at location 5 (Table 6), suggesting predominance of viral and/or bacterial pathogens. Bacteria are the pathogen group most sensitive to chlorination, followed by enteric

viruses, while protozoa are most persistent (Petterson and Stenström, 2015).

4.7. Limitations

Limitations included the study design and potential confounding. Time series studies are a type of ecological study based on passive observation of groups, so individual exposure is not well controlled (Hunter et al., 2003). Misclassification of exposure is possible, because individuals likely move throughout the day, using multiple drinking water sources (including bottled and stored tap water) from work, home, school, and other public locations. The correspondence between the water service area and the municipalities where health data were measured was also less than 100% for location 3. Water quality indicators (e.g., turbidity, free chlorine) used in this study likewise do not measure pathogen presence directly, but serve as more readily measurable surrogates for exposure. The outcome measure is probably affected by missing data (Bounoure et al., 2011), especially for mild acute gastroenteritis cases treated at home. Additional indicators (e.g., high-resolution water quality data from distribution systems, self-reported consumption) were not typically available to confirm all steps in the theoretical causal chain from water contamination to consumption to symptom development and reporting.

Study limitations may have led to underestimation of relative risk. Although all variables were not tested beyond a 15-day time lag in France and 1-month time lag in Spain, multiple windows of potential significance (Table 5) and sensitivity test results suggest variable rates of secondary contagion and/or the presence of multiple pathogens or pathogen types, such as viruses, bacteria, and protozoa (Aramini et al., 2000; David et al., 2014; Egorov et al., 2003; Gilbert et al., 2006). Selecting the one or two most significant time lags could thus underestimate impact relative to including a larger range (e.g., up to 30 days) that captures all primary and secondary cases (Aramini et al., 2000; Beaudeau, 2003). The pooled one-month lag window (ranging from about 30–60 days prior to case reporting) at location 5 may have more effectively captured secondary cases and multiple pathogen types, including *Cryptosporidium* and *Giardia*. Finally, while seasonal controls help to account for dominant exposure routes (e.g., person-to-person transmission), they may filter out consistent seasonal variations in water-related exposures.

Overestimation of population-level risks is also possible. Predominant acute gastroenteritis risk likely stems from foodborne and person-to-person transmission routes in these settings, and multiple factors could contribute to a single case of acute gastroenteritis. Controls were applied to filter out background levels as much as possible and isolate the signal related in full or part to drinking water exposure. The reported rate ratios best approximate relative risk for small effect sizes (within 20% of the null value). Attribution of risk is most appropriate when the exposure of interest causally influences the outcome, and this may not hold true for all exposure measures across all locations (De Roos et al., 2017; Tam et al., 2007). The same pathogen exposure level may not lead to illness in all individuals, based on immune function and susceptibility. Further, some degree of disease burden may be intractable and not amenable to intervention.

4.8. Implications and recommendations

In accord with other research (Baum et al., 2016; Hrudey and Hrudey, 2007), this study offers evidence that the status quo in high-income countries carries some waterborne disease risk, and efforts to optimize risk management programs are warranted. WSPs can be applied both to improve steady state conditions and to reduce outbreaks. Risk prevention may involve both "hard" technological solutions and "soft" management components, such as improved coordination or behavior change (Bartam et al., 2009; Loret et al., 2016). Risk management strategies include mitigation, transfer, avoidance, and

acceptance. While some hazards (e.g., weather) cannot be altered, treatment approaches can be refined to address known risks. Many water suppliers have already committed to preventive management to minimize risks (WHO and IWA, 2017). Since early 2018, the revised European Union (EU) Drinking Water Directive requires proactive risk management at all EU drinking water utilities (European Parliament Council, 2018). These scale-up efforts may benefit from evidence around best practices.

While risk management programs have the potential to produce benefits, implementation can vary widely in practice. Implementers of WSPs should be aware of potential pitfalls, such as "tokenism," poor fidelity, or poor long-term adherence to the WSP program (Rondi et al., 2015; Summerill et al., 2010). A culture of iterative quality improvement and learning from "near misses" can support ongoing WSP performance (Bereskie et al., 2017; Takala and Heino, 2017). Periodic monitoring and evaluation should be built into programs to ensure public health and other goals are being achieved. Attention to measuring implementation outcomes as well as direct outcomes of the intervention may be warranted (Gelting et al., 2012; Proctor et al., 2011). Improved awareness of common pathogens and water supply contamination routes can benefit development and redevelopment of site-appropriate critical controls.

Owing to connections between waterborne disease risk and climate patterns, risk management approaches should consider potential hazards posed by climate change (Bartram et al., 2017; Beaudeau et al., 2011; Chhetri et al., 2017; Howard et al., 2016; Levy et al., 2016). Of the three locations studied, location 5 is subject to the greatest projected climate change and social sensitivity to climate change, due in part to flash floods and urban heat island effects (European Commission, European Environment Agency, 2018). Significant relationships between weather patterns and acute gastroenteritis were observed at all locations (Table 6). Coupled with case observation of increased immigration to cities (affecting socioeconomic status), more intensive development (affecting nonpoint source pollution), and water scarcity, results suggest waterborne disease risks may require more attention in the future.

This study design was selected to improve on a previous observational study (Setty et al., 2017) and achieve parallels to a case-control study (Hunter et al., 2003; Lu and Zeger, 2007). While a number of suspected influences were accounted for, future models could seek to address missing components of the causal chain between drinking water exposure and health outcomes. For example, daily microbial indicator measurement in raw water might help to identify changes in upstream pathogen loading from the watershed, wastewater discharge, or sediment resuspension. Capturing geospatial relationships between distributed water quality and disease reporting locations is another potential mechanism for model improvement. Wider availability of pathogen-specific disease data could benefit future research (Levy et al., 2016). Future studies involving weather might also incorporate relative humidity, which may be a predictor of survival for some pathogens and exposure pathways (Fisman et al., 2005; Lowen and Steel, 2014).

Longer-term impacts of WSP implementation, such as water quality and health improvements, may be observed later than changes in inputs, activities, and outputs (Gelting et al., 2012). Clarification of "leading" versus "lagging" indicators more broadly (Proctor et al., 2011) would benefit future study, especially by clarifying the minimum time needed for observing improved health outcomes after WSP certification. Lengthier post-implementation monitoring periods (e.g., more than two years) might increase statistical power for evaluation studies, but could reduce speed in working through iterative improvement cycles (Bereskie et al., 2017; Gunnarsdottir et al., 2012a). Establishing linkages between or among inputs, activities/outputs, outcomes, and impacts in the WSP evaluation framework (Gelting et al., 2012), such as determinants of operational changes and health improvements, would also provide valuable insight into effective implementation strategies (Powell et al., 2017).

5. Conclusions

This study further clarified the mechanisms by which proactive drinking water management interventions (such as WSPs) can influence public health outcomes. It quantified relationships between drinking water exposure parameters and acute gastroenteritis outcomes at three locations in France and Spain. Findings add to the knowledge base for refining individual utility practices and regional WSP implementation strategies. Weather patterns, particularly dry periods followed by heavy rain, were significantly associated with acute gastroenteritis rates for the location supplied by surface water. The treatment approach used since 2010 may have sufficiently mitigated this risk to explain the previously observed health improvement. For the groundwater location, increased acute gastroenteritis rates corresponded to daily peaks in the turbidity of finished water. WSP controls on chlorine levels appear to have altered the turbidity-risk relationship, although this did not correspond to public health improvement.

Site-specific time series models may be applied to assist risk management planning across a range of public health surveillance data types. Despite aggregated monthly health data, the location using both surface and groundwater demonstrated a significant harmful association with higher average turbidity, finished water flow rates, and precipitation, as well as a protective association with free chlorine measured at the plant outlet. These associations offer insight to help refine water supply management (e.g., groundwater versus surface water use) and WSP controls at the Spanish location. While average turbidity decreased in a previous study, intermittent peaks may have been more closely related to the observed health outcomes. Continued observation and investigation of synergies is recommended to inform iterative improvement of the WSPs and eventual achievement of public health benefits. Differences among the three locations examined make the findings context-specific, although the insights gained may benefit management of other chlorinated drinking water treatment systems in high income countries.

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