Full length article

Association between meteorological factors and hepatitis A in Spain 2010–2014

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ARTICLE INFO

ABSTRACT

Background: There is growing concern of how climate change could affect public health, due to the increase number of extreme climate events. Hence, the study of the role that climate events play on the distribution of waterborne diseases, like Hepatitis A, could be key for developing new prevention approaches.
Objective: To investigate the association between climate factors and Hepatitis A in Spain between 2010 and 2014.
Methods: Weekly Hepatitis A cases between 2010 and 2014 were obtained from the Spanish Epidemiology Surveillance Network. Climate variables (weekly cumulative rainfall, rainy days, storm days and snow days) were obtained from National Climatic Data Center (NOAA satellite and information Service of USA). Each municipality was assigned to the nearest weather station ($N = 73$). A Mixed-Effects Poisson regression was performed to estimate Incidence Rate Ratios (IRR), including a time lag of 2, 3 and 4 weeks (most probable incubation period for Hepatitis A).
Results: Rainfall higher than 90th percentile (extreme precipitation) was associated with increased number of Hepatitis A cases 2 weeks (IRR = 1.24 CI 95% = 1.09–1.40) and 4 weeks after the event (IRR = 1.15 CI 95% = 1.01–1.30). An extra rainy day increased the risk of Hepatitis A two weeks after (IRR = 1.03 CI 95% = 1.01–1.05). We found higher risk of Hepatitis A two weeks after each extra storm day (IRR = 1.06 CI 95% = 1.00–1.12), and lower risk with 3 and 4 weeks' lag (IRR = 0.93 CI 95% = 0.88–0.99 for lag3; IRR = 0.94 CI 95% = 0.88–0.99 for lag 4).
Conclusions: There is an increased risk of Hepatitis A 2 weeks after water-related climate events. Including meteorological information in surveillance systems might improve to develop early prevention strategies for waterborne diseases.

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1. Background

Hepatitis A is a self-limited liver disease caused by the infection of Hepatitis A virus (HAV). HAV is transmitted via the fecal-oral route, directly from person-to-person or indirectly by ingestion of feces-contaminated food or water (Previsani and Lavanchy, 2000). The disease is a typically food-waterborne disease because HAV is abundantly excreted in feces and it can survive in the environment for prolonged periods of time (Previsani and Lavanchy, 2000). Direct person-to-person dissemination is common under poor hygienic conditions. Its incubation period varies between 14 and 28 days, but it can last 50 days (Desenclos et al., 1991).

Infections occur early in life in areas where sanitation is poor and living conditions are crowded. With improved sanitation and hygiene, infections are delayed and consequently the number of people susceptible to the disease increases. Under these conditions, explosive epidemics can arise from fecal contamination of a single source. In most industrialized nations, where hepatitis A is no longer considered a childhood disease, infections with HAV are increasingly contracted by adults. According to The European Surveillance System (TESSy), the notification rate in the EU/EEA has fallen between 1997 and 2011, from 10.0 to 2.5 per 100,000 population (Gossner et al., 2015).

In Spain, Hepatitis A is a compulsory notifiable disease and individual cases are reported to the National Epidemiological Surveillance Network (Red Nacional de Vigilancia Epidemiológica, RENAVE). All

Spanish Regions recommend selective HAV vaccination for the people at highest risk, following the recommendations of the Spanish Ministry of Health; moreover, Catalonia Region and the Autonomous cities Ceuta and Melilla include systematic HAV vaccination in their calendars (Domínguez et al., 2003). In 2014, the annual incidence of Hepatitis A was slightly >1 case /100,000 population according to the latest reports of RENAVE (Centro Nacional de Epidemiología, 2016). There is high space-time variability in the incidence of Hepatitis A, and it has been hypothesized that this variability could be due to some extent to climate exposure variability (Gomez-Barroso et al., 2012).

Global climate change is expected to affect the frequency, intensity and duration of extreme water related weather events such as excessive rainfall, storm surges, floods, and drought (Semenza and Menne, 2009). During periods of heavy precipitation, local water quality can be seriously compromised via diverse means, a significant one being the cross-contamination of water sources due to infiltration and inflow between sewage and water pipes. The effect of climate and environmental factors (weather conditions, such as temperature, rainfall, and relative humidity), on waterborne disease incidence has been explored in different studies (Cann et al., 2013; Guzman Herrador et al., 2015; Wu et al., 2016). However, the impact of these environmental factors on Hepatitis A incidence remains unclear, as few studies have studied the specific effect on Hepatitis A (Chen et al., 2012), although there are some insights of this associations as different outbreaks of Hepatitis A after water-related weather events have been reported (Guis et al., 2006; Lee et al., 2008; Sowmyanarayanan et al., 2008).Our hypothesis is that there will be an increased risk of Hepatitis A after water-related events (rain, storm, snow), taking into account the incubation period. Thus, the objective of this research is to investigate the association between climate factors and incidence of Hepatitis A in Spain between 2010 and 2014.

2. Methods

2.1. Setting

According to the Spanish Statistical Office Municipal registry (Instituto Nacional de Estadística, INE) Spain had a population of nearly 47 million people in 2014, distributed in 8116 municipalities. The population varies from municipalities with 1 inhabitant to municipalities with over 3,000,000 inhabitants. The average population density was 93.51 inhabitants/km^2. These municipalities are aggregated into 52 provinces which in turn are aggregated in to 17 autonomous regions and two autonomous cities. The area of Spain is 504,645 km^2.

The climate of Spain is extremely spatially variable. According to the Köppen classification, Spain has Dry Climates (type B) in the southeast of the Peninsula Iberica as well as the Ebro Valley, and some parts in the southern central plateau region, Extremadura and the Balearic Islands; temperate climates (type C, where the average temperature in the coldest months is between 0 and 18 °C) covers almost 40% of the country, including the majority of the southern central plateau region, and the Mediterranean coastal regions, with the exception of the arid zones in the southeast, Cold Climates (type D) are located in small areas of the mountainous regions at higher altitudes in the Cantabria Mountains, the Iberian Mountain Ranges, Central Ranges and the Sierra Nevada (Agencia Estatal de Meteorología, 2011).

2.2. Data collection

All individualized cases of Hepatitis A reported to RENAVE for the period 2010–2014 were initially included (aggregated epidemiological data is available through the surveillance report in: http://www.isciii.es/ISCIII/es/contenidos/fd-servicios-cientifico-tecnicos/fd-vigilancias-alertas/fd-enfermedades/enfermedades-declaracion-obligatoria-informes-anuales.shtml). Each case includes information of age, sex, municipality of case assignment, reporting week and case classification data. We excluded from our analysis cases with incomplete of non-existent information about age, sex, municipality, or notification week. Total population for each municipality stratified by age and sex was obtained in the continuous municipality census track in 2014, provided by the INE. Each case was assigned to the UTM coordinates, datum 50 (x,y) of the centroid of the municipality.

Climate daily data over the same period were obtained from National Climatic Data Center NOAA (US Department of Commerce NS and IS, 2016). Daily data were grouped weekly to obtain weekly cumulative rainfall, weekly rainy days, weekly storm days and weekly snow days. Storm day is defined as a day with electrical activity as thunders (Agencia Estatal de Meteorologia, 2015). As the NCDC report climate data by weather station, each municipality was assigned to the nearest weather station. Therefore, 73 meteorological regions were created (Fig. 1). We only took data from stations that have, at least, 95% of the daily climate data completed. Where a day was found to have missing data, this was replaced by a four-day moving average centered on that day.

2.3. Statistical analysis

First, descriptive statistics were calculated for Hepatitis A and climate data, providing incidence estimates of Hepatitis A by sex and year. Mean, standard deviation and quartiles are provided for weekly cumulative rainfall, weekly rainy days, weekly storm days and weekly snow days. Due to the distribution of the weekly cumulative rainfall, in the further analysis was treated as dichotomous; thus, we test for "extreme precipitation", defined as cumulative rainfall higher than the 90th percentile of the weeks.

A Mixed-Effects Poisson regression was created to study the relationship between Hepatitis A cases and climate factors. As the dependent variable, Hepatitis A cases were included. In the fixed part of the
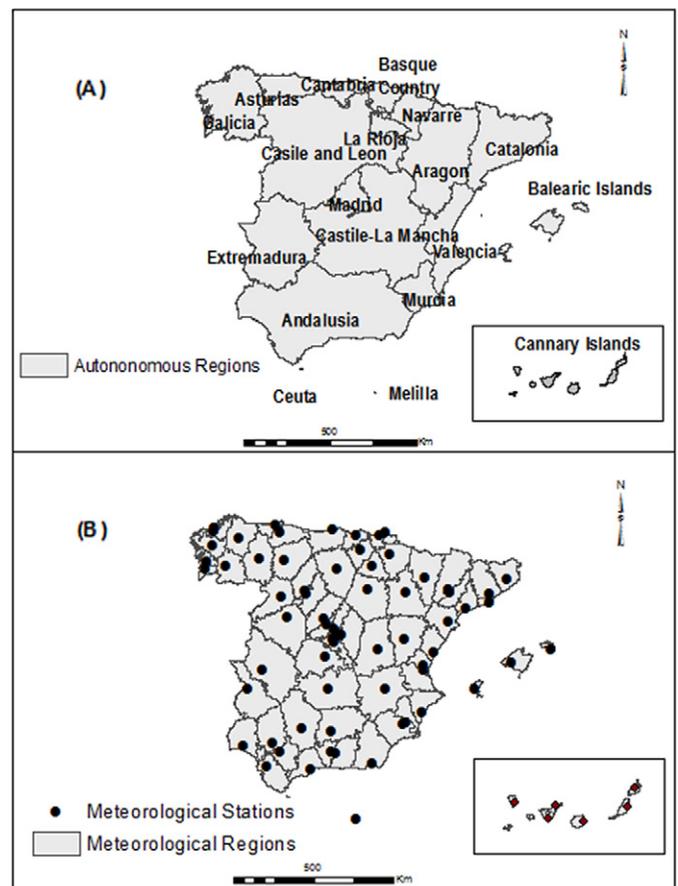

Fig. 1. Map of the Autonomous Regions of Spain (A) and the distribution of the meteorological stations and the meteorological regions created (B).

equation, climate factors, with a time lag of 2, 3 and 4 weeks (most probable incubation period for Hepatitis A), were included, and the meteorological station was introduced as the random part of the model. We also included time trend and an offset of the population logarithm in the model. We estimated Incidence Rate Ratio and 95% Confidence Intervals. As a sensitivity analysis, due to some over-dispersion of the dependent variable (variance was slightly greater than the mean), we repeated the analysis using negative binomial regression instead of Poisson, with no significant differences in our estimates.

In a first step, we created models for each of the lag time lags, and then, a multivariate model with the 2, 3 and 4 time lags. Separate models were created for each of the climate factors (weekly cumulative rainfall, weekly rainy days, weekly storm days and weekly snow days) due to collinearity between climate factors. All analyses were conducted using Stata SE version 14.1 (StataCorp., College Station, TX, USA). All GIS-related operations were undertaken with ArcGIS 10.0 software (ESRI, Redlands, CA, USA).

3. Results

3.1. Description of the incidence of Hepatitis A

Between the first week of January 2010 and the last week of December 2014, 3674 cases of Hepatitis A were reported to RENAVE. 226 cases (6.1%) were excluded as no information about sex, age or municipality was found (final cases = 3448). 41.59% of the cases were women, and the mean age was 24.48 years. Crude annual incidence was 1.48 cases/100000 habitants (Fig. 2). There has been a significant decrease in the incidence of Hepatitis A between 2010 and 2014; specifically, in 2010 the incidence of Hepatitis A was 2.12 cases/100,000 inhabitants and, in 2014, the incidence was 1.09 cases/100,000 inhabitants. The spatial distribution of the incidence showed regional differences in the incidence of Hepatitis A (Fig. 3); eastern parts of Spain showed higher incidence. There is seasonal variability in the cases of Hepatitis A. In winter there were more Hepatitis A cases; >30 cases of Hepatitis A were declared in some winter weeks (Fig. 4).

3.2. Description of the climate variables

The weekly cumulative rainfall by meteorological region ranged from 0 to 553.21 mm (Table 1). The median was 0.76 mm and the 90th percentile 30.48 mm. >25% of the weeks there was no rainy days (25th percentile = 0 days; 50th percentile = 1 day). Weekly storm and snow days ranged from 1 to 6 days (mean 0.21 and 0.07 days respectively). Autumn and winter are the seasons with higher precipitation through the 5-year series (Fig. 4).
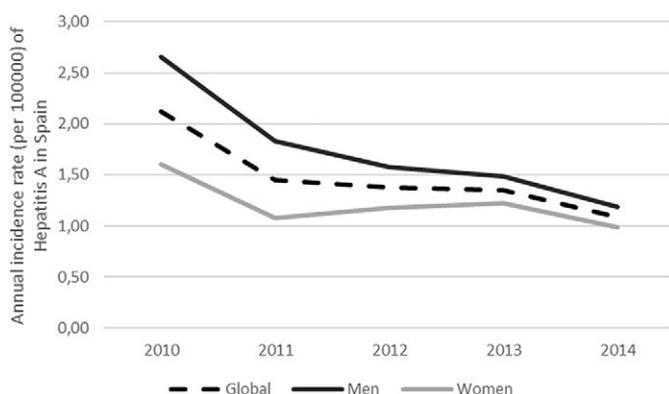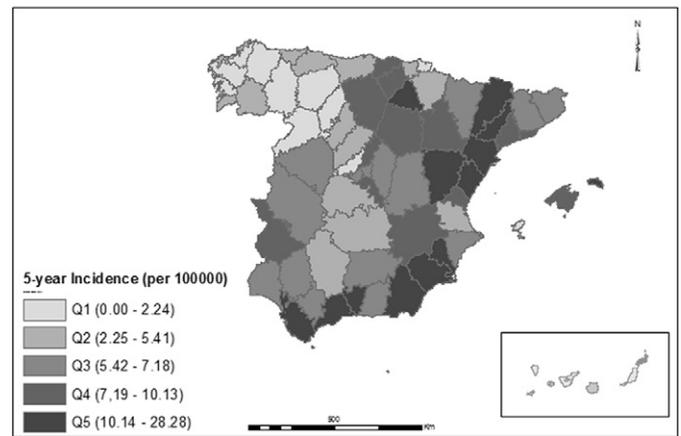

Fig. 3. Map of the 5-year incidence of Hepatitis A for each meteorological region in Spain between 2010 and 2014.

3.3. Association between climate factors and Hepatitis A

The results of the regression analyses are displayed in Table 2 and Fig. 5. In the univariate analysis, there was a significant 24% higher risk of Hepatitis A two weeks after an extreme precipitation week (IRR = 1.24 CI 95% = 1.09–1.40). With a 3 weeks' lag, there was no relationship between extreme precipitation and Hepatitis A (IRR = 1.03 CI 95% = 0.91–1.18), while 4 weeks after, there was a 15% higher risk of Hepatitis A (IRR = 1.15 CI 95% = 1.01–1.30). In the multivariate analysis, after taking into account all time lags, the relationship remained significant for the 2 weeks' lag (IRR = 1.22 CI 95% = 1.07–1.38), and stayed in the limit of statistical significance for lag 4 (IRR = 1.13 CI 95% = 1.00–1.29).

An extra rainy day increased the risk of Hepatitis A two weeks after by 3% (IRR = 1.03 CI 95% = 1.01–1.05) both in the univariate and multivariate analysis. No association was found between weekly rainy days and Hepatitis A for the 3 and 4 weeks' lag (Table 2). We found a 6% higher risk of Hepatitis A two weeks after each extra storm day in the univariate analysis (IRR = 1.06 CI 95% = 1.00–1.12), which remained in the multivariate model (IRR = 1.07 CI 95% = 1.01–1.13). Storm days were associated with lower risk of Hepatitis A with 3 and 4 weeks' lag, both in the univariate (IRR = 0.93 CI 95% = 0.88–0.99 for lag3; IRR = 0.94 CI 95% = 0.88–0.99 for lag 4) and the multivariate models (IRR = 0.93 CI 95% = 0.87–0.99 for lag3; IRR = 0.94 CI 95% = 0.88–1.00 for lag 4). No association was found in the univariate analysis for weekly snow days and Hepatitis A; however, in the multivariate analysis, an extra snow day increased the risk of Hepatitis A by 16% (IRR = 1.16 CI 95% = 1.03–1.30).

4. Discussion

As far as we know, this is the first quantitative analysis of the relationship between climate factors and Hepatitis A in Spain and Europe, considering both spatial and temporal components. Extreme precipitation was associated with increased two-weeks-after rates of Hepatitis A notifications between 2010 and 2014 in Spain. This association was found to be significant in the unadjusted univariate analysis and remained significant after adjusting for the rest of the time lags. Besides, rainy, storm and snow days were associated with higher risk of Hepatitis A two weeks after. On the other hand, more storm days were associated with less risk of Hepatitis A 3 and 4 weeks after.

The relationship between climate factors and waterborne diseases has been studied before, as different reviews have pointed out in the last years (Cann et al., 2013; Guzman Herrador et al., 2015). These reviews highlighted that, in general, extreme precipitation increases the risk of diarrhea and waterborne diseases. However, the most common
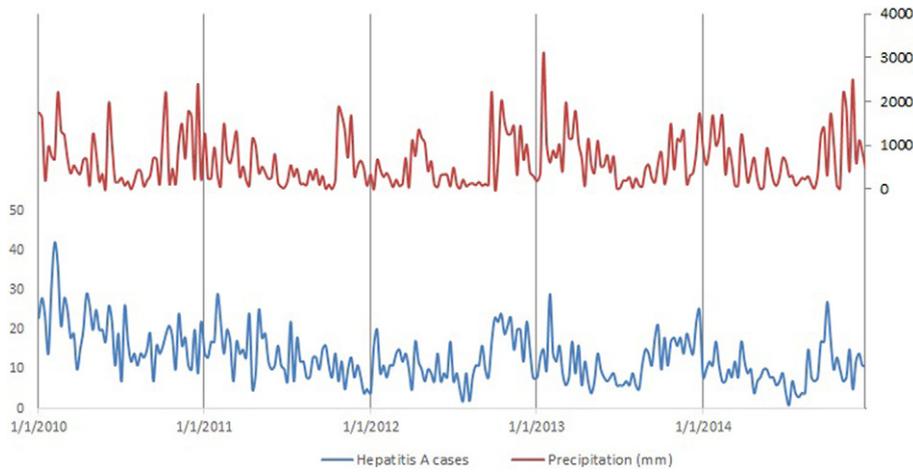

Fig. 2. Description of the global incidence of Hepatitis A in Spain between 2010 and 2014, for men and for women.

Fig. 4. Hepatitis A total number of cases (lower line) and mean precipitation for all the stations (mm) (upper line) between 2010 and 2014.

approach is to study cases of gastrointestinal infections without specifying the type of microorganism. Thus, a deeper understanding on the specific type of microorganism affected by climate events could provide insights of the specific mechanisms behind. When addressing this issue, most studies had their focus on pathogens like *Vibrio* spp. and *Leptospira* spp. (Cann et al., 2013) or *V. cholerae* (Guzman Herrador et al., 2015), finding a relationship between climate events and the incidence of these diseases. However, there are few studies who had a focus on Hepatitis A; for instance, a study in Rio de Janeiro (Villar et al., 2002) found that rainy season was associated with higher risk of Hepatitis A; while Chen et al. (Chen et al., 2012) found no association between rainfall and Hepatitis A. Despite this fact, several outbreaks of Hepatitis A have been reported in scientific literature (Guis et al., 2006; Lee et al., 2008; Sowmyanarayanan et al., 2008) and ProMED after water-related weather events (Cann et al., 2013). However, none of these studies have considered the effect of spatial variation within the region, which we solved by using a mixed-effects regression model.

Periods of extreme precipitation can compromise the quality of the local water supplies which, in the end, may cause higher risk of Hepatitis A as well as other waterborne infectious diseases. Although well-managed public water supply systems are expected to be able to cope with weather extremes, such extremes can cause both physical and managerial stress which may impact water quality. Aging water treatment and distribution systems are particularly susceptible to heavy precipitation events, increasing the vulnerability of the drinking water supply (Guzman Herrador et al., 2015). Public health practitioners and water companies should be aware of the risks of waterborne disease outbreaks following these events (Hurst et al., 2004; Solomon et al., 2007); both the World Health Organization (WHO) and the European Centre for Disease Prevention and Control (ECDC) have emphasized the need for strengthening partnerships between health and climate experts, to improve scientific evidence of the linkage between health and climate drivers (Semenza and Menne, 2009; World Health Organization, World Meteorological Organization, 2012). Pascal et al.

(2012) have advocated in favor of introducing a perspective of climate change into epidemiological surveillance; for instance, by monitoring climate-related indicators to provide early warnings and to inform decision-making (Pascal et al., 2012).

It was not expected that a negative association between storm days and 3 and 4 weeks-after risk of Hepatitis A. Although some authors have argued that periods of low precipitation may cause an increased risk of waterborne diseases (Semenza and Menne, 2009), storm days might not be a good indicator for waterborne diseases, as the definition that we used implies "electrical activity and thunders" (Agencia Estatal de Meteorologia, 2015) which not necessary always include water accumulation. Moreover, weeks with more storm days could be related with few water accumulation in the following days, which in turn could decrease the risk of Hepatitis A for the lags of 3 and 4 weeks.

The impacts of extreme water-related weather events on waterborne diseases may affect certain populations and will likely contribute to health disparities (Curriero et al., 2001). The ability of a population to adapt and limit the effects of such events is likely to depend on socio-economic and environmental circumstances as well as the availability of information and technology (Solomon et al., 2007). Less developed regions may be at greater risk due to lower adaptive capacity. Future studies should incorporate a health-disparities perspective in understanding how climate conditions may affect certain populations. In our study, we were not able to adjust for socioeconomic variables, as the use of surveillance information limits the information to the basics (age, sex and geographical location).

In testing how diseases are related with prior rainfall, methodology is crucial. To avoid multiple testing and the likelihood of spurious associations, we only checked for the variables and lags that we thought, based on literature review, that would be important. There are different ways for measuring extreme precipitation, and there is no consensus in which may be the best measure, as it will depend on the local context (Guzman Herrador et al., 2015). As there is no agreement for which may be considered as "extreme precipitation" in Spain, we chose a

Table 1
Descriptive statistics on climate variables in Spain between 2010 and 2014.

| | Percentiles, mean and standard deviation (SD) | | | | | | | | | | |
	Min	5th	10th	25th	50th	75th	90th	95th	Max	Mean	SD
Weekly cumulative rainfall (mm)	0	0	0	0	0.76	10.41	30.48	48.26	553.21	9.89	20.89
Weekly rainy days	0	0	0	0	1	3	5	5	7	1.85	1.85
Weekly storm days	0	0	0	0	0	0	1	1	6	0.21	0.55
Weekly snow days	0	0	0	0	0	0	0	1	6	0.07	0.39

Table 2
Association of climate factors with Hepatitis A in Spain between 2010 and 2014 estimated by mixed-effects Poisson regression.*

Climate exposure	Time lag (weeks)	Univariate model		Multivariate model	
		IRR*	CI 95%	IRR*	CI 95%
Extreme precipitation	2	**1.24**	**1.09–1.40**	**1.22**	**1.07–1.38**
	3	1.03	0.91–1.18	1.00	0.88–1.44
	4	**1.15**	**1.01–1.30**	**1.13**	**1.00–1.29**
Rainy days	2	**1.03**	**1.01–1.05**	**1.03**	**1.01–1.05**
	3	1.00	0.98–1.03	1.00	0.97–1.02
	4	1.01	0.99–1.03	1.01	0.99–1.03
Storm days	2	**1.06**	**1.00–1.12**	**1.07**	**1.01–1.13**
	3	**0.93**	**0.88–0.99**	**0.93**	**0.87–0.99**
	4	**0.94**	**0.88–0.99**	0.94	0.88–1.00
Snow days	2	**1.09**	**0.98–1.22**	**1.16**	**1.03–1.30**
	3	0.88	0.77–1.03	0.88	0.76–1.02
	4	1.00	0.89–1.13	1.00	0.89–1.14

* IRR = Incidence Rate Ratio. Bold: $p < 0.05$.

cut-off point at the 90th percentile, as it has been used in another research (Curriero et al., 2001). Nevertheless, the decision of the cut-off point may condition to find (or hide) an association.

We acknowledge that this study has some limitations. Notification rate at national level may vary widely between regions and it could introduce a bias; for instance, some regions notify Hepatitis A cases with missing information (municipality, age, sex) that were not included in the analysis. Also, using notification data from surveillance analysis might underestimate the real incidence of Hepatitis A. However, this sub-notification would affect the results only if it is related with our exposure (e.g. sub-notification is higher after 2, 3 or 4 weeks of extreme precipitation), which is very unlikely. Besides, we recognize that multiple factors are involved, which must occur simultaneously in time and space. These elements include (1) a source of contamination; (2) fate and transport of the contaminant from source to drinking water supplies; (3) inadequate treatment; and (4) reporting of the case. Besides, other factors can affect the occurrence of Hepatitis A: sexual relationships, public health services or population demographics, among others.

Spatial auto-correlation was not adjusted for in the analysis so there is the potential that this may have affected the estimation of the standard errors. Also, it should be considered that cases were attributed to the municipality where the infection took place; however, in some cases the notified municipality was the residence municipality. The exact date of onset of symptoms was not available, only the week of notification was recorded. However, as Hepatitis A has a long incubation period and we took from 2 to 4 weeks as a lag period, we do not considered that it should affect our results.

5. Conclusions

Extreme rainfall, weekly days of rainfall, and snow are associated with a higher risk of Hepatitis A two weeks later in Spain between 2010 and 2014. These results show that there is a need for strengthening partnerships between health and climate experts; thus, epidemiological surveillance systems might be benefited from the integration of meteorological data in order to develop early prevention strategies for waterborne diseases.

Competing interests

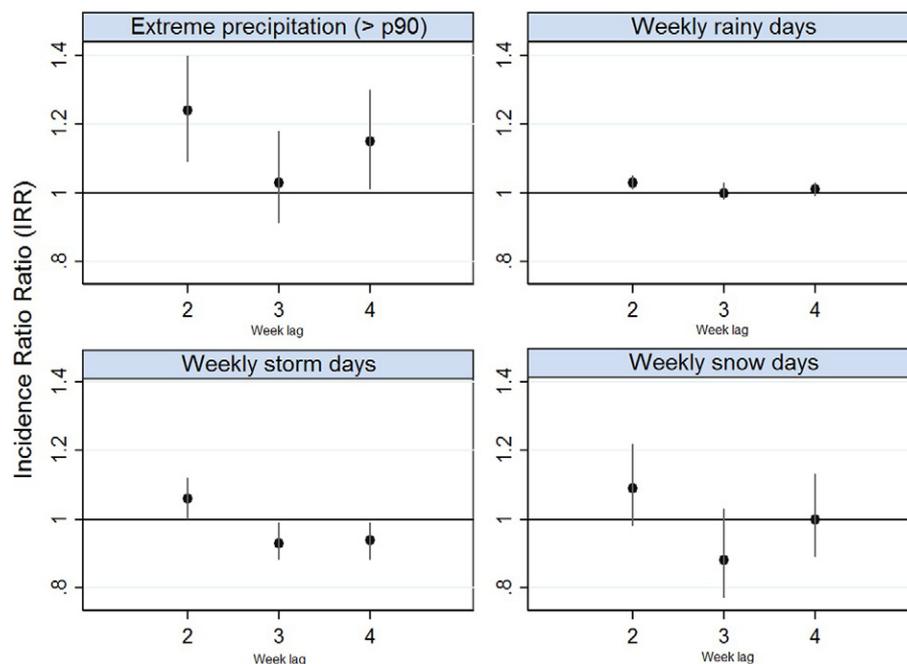All authors report no competing or conflict of interest.

Fig. 5. Incidence Rate Ratio (IRR) as estimated by the mixed-effects poisson regression for the association of climate factors with Hepatitis A in Spain between 2010 and 2014.

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