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West Nile Virus infection in Northern Italy: case-crossover study on the short-term effect of climatic parameters.

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Short title: West Nile Virus and climatic parameters in Italy

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Abstract:

Background: Changes in climatic conditions are hypothesized to play a role in the increasing number of West Nile Virus (WNV) outbreaks observed in Europe in recent years.

Objectives: We aimed to investigate the association between WNV infection and climatic parameters recorded in the 8 weeks before the diagnosis in Northern Italy.

Methods: We collected epidemiological data about new infected cases for the period 2010-2015 from the European Center for Disease Control and Prevention (ECDC) and meteorological data from 25 stations throughout the study area. Analyses were performed using a conditional Poisson regression with a time-stratified case-crossover design, specifically modified to account for seasonal variations. Exposures included weekly average of maximum temperatures, weekly average of mean temperatures, weekly average of minimum temperatures and weekly total precipitation.

Results: We found an association between incidence of WNV infection and temperatures recorded 5-6 weeks before diagnosis (Incidence Rate Ratio (IRR) for 1°C increase in maximum temperatures at lag 6: 1.11; 95% CI 1.01-1.20). Increased weekly total precipitation, recorded 1-4 weeks before diagnosis, were associated with higher incidence of WNV infection, particularly for precipitation recorded 2 weeks before diagnosis (IRR for 5 mm increase of cumulative precipitation at lag 2: 1.16; 95% CI 1.08-1.25).

Conclusions: Increased precipitation and temperatures might have a lagged direct effect on the incidence of WNV infection. Climatic parameters may be useful for detecting areas and periods of the year potentially characterized by a higher incidence of WNV infection.

Key Words: West Nile Virus, Temperatures, Precipitations, Lag-distributed Models, Case-crossover

1. Introduction

West Nile Virus (WNV) is a globally distributed RNA virus of *Flaviviridae* family (Campbell et al. 2002). It is maintained in nature through an enzootic cycle. Adult mosquitoes, generally of *Culex* genus, represent primary bridge vectors, while susceptible bird species play the role of amplification hosts (Chancey et al. 2015). Humans usually develop infection after being bitten by an infected mosquito. Infection in humans is generally asymptomatic, but 20% of infected subjects can develop a febrile syndrome, known as West Nile Fever (WNF), and less than 1% of infected subjects can develop a West Nile Neuroinvasive Disease (WNND) characterized by encephalitis or meningitis symptoms (David and Abraham 2016).

In recent years, several outbreaks of WNV infection have been recorded in many European and Mediterranean countries (Rizzoli et al. 2015). Infected migratory birds are responsible for the introduction of the virus in new areas, while native mosquitoes feeding behaviour, presence of susceptible endemic birds and local environmental conditions are essential for persistence and amplification of the virus in new areas (Reisen and K. 2013, Rizzoli et al. 2015). Climatic and meteorological conditions have been suggested as important factors for virus transmission in newly affected areas (Paz 2015a; Paz et al. 2013). High extrinsic temperatures are associated with virus replication and the growth rate of the vector population (Gubler et al. 2001). Levels of precipitation are also believed to play an important role in pathogen/vector ecology: some studies reported that vector replication and activity are positively associated with heavy rainfall and other studies reported that mosquitoes' abundance is associated with drought periods (Nile et al. 2009, Paz 2015).

In Italy, the WNV was isolated for the first time in 1998 in 14 equine cases and the first human case was identified in 2008. Since then, human cases of WNV infection have been repeatedly notified, and now the virus is considered endemic in Italy (Rizzo et al. 2016). Concurrently the number of provinces set in Northern Italy affected by WNV circulation has increased during the study period (3 provinces in 2010 vs 16 in 2015). Thus, Italy can be considered as an example of area that is facing the process of endemization of an emerging pathogen.

The purpose of this study is to evaluate the short-term effects of air temperatures and precipitation on the incidence of WNV infection to understand the role of climatic parameters in the spread of WNV infection in an area, such as Northern Italy, where the process of endemization has recently started.

2. Methods

2.1 Data collection and elaboration

Epidemiological data were obtained from the European Center for Disease Control and Prevention (ECDC). In our study, WNV cases are subjects resident in Northern Italy who, during the period 2010-2015, met the European criteria for probable or confirmed case of WNV infection (European Commission Decision 2008/426/E). Cases are confirmed if at least one following laboratory criterion is present: isolation of WNV from blood or Cerebrospinal Fluid (CSF), detection of WNV nucleic acid in blood or CSF, WNV specific IgM in CSF, WNV IgM high titer and subsequent detection of WNV IgG. Cases are considered probable in presence of stable and elevated virus specific serum antibody titer in association with one clinical criterion (fever, meningitis or encephalitis) or evidence of an epidemiological link that proves animal/human to human transmission. Thus, notified cases recorded by ECDC are a heterogeneous population and include: WNV positive blood donors, cases of WNF and cases of WNND. For each case, the ECDC provides information on the year, the week and the geographical province of diagnosis.

Meteorological data were obtained from the Regional Environmental Protection Agency (ARPA) for each province that reported at least one case of infection between 2010 and 2015. We used the information recorded by the land-based meteorological stations set in the capital of each province. Meteorological data included minimum, mean, maximum daily temperatures, and daily precipitation. On the daily data of temperatures and precipitation a quality control was carried out to exclude the possibility of measurement error (Fortin et al 2017; Acquaotta et al, 2016; Zandonadi et al, 2016). In order to conform meteorological data to epidemiological data, we calculated the weekly average of the minimum, mean and maximum temperatures, as well as, the weekly total precipitation. We considered missing all weeks with at least one missing daily information (information missing on weekly scale: 4.4% for maximum temperatures, 6.4 % for mean temperatures, 5.1% for minimum temperatures and 6.1% for total precipitation).

2.2 Study design

To estimate the association between climatic parameters and WNV infection, we used a case-crossover design, which is a special case-control design where every case serves as its own control and originally developed to study the acute effect of transient exposures on the risk of rapid onset events (Maclure and Mittleman 2000). For each case, exposures occurring during the period prior to the event (known as "hazard period") are compared to exposures at comparable control periods (known as "reference periods") (Janes et al. 2005a; Janes et al. 2005b, Levy et al. 2001). In our study, control periods were identified according to a time-stratified sampling scheme, which uses fixed and relatively short time strata (e.g. calendar month) to match case and control periods (e.g. calendar week). Time-stratified case-crossover design has been repeatedly applied in environmental studies as it can control for long time trends (e.g. variability from year to year) and seasonality (variability from month to month) and can provide results equivalent to time series regression (Bateson and Schwartz 1999; Navidi 1998; Lu and Zeger 2007). We further modified the original time-stratified approach with the inclusion of a b-spline function of time to control for residual temporal variation within strata, given the strong seasonality of WNV infection (Whitaker et al. 2007).

After observing the 2010-2015 cumulative epidemic curve, we firstly defined the transmission period of WNV, identifying the time interval going from the 27th to the 46th weeks of each year (length of 20 weeks). We secondly divided the identified period into 5 strata, each of 4 weeks length. For each week in which at least one human WNV case was reported (case period), we selected the other 3 weeks of the stratum as control periods. Exposure to meteorological variables, recorded in the capital of the province, were attributed to each case on the basis of the province in which her/his diagnosis was made.

2.3 Statistical analysis

The analysis was performed using conditional Poisson regression (Armstrong et al. 2014). Since weather effects on infectious disease risk may be delayed (lag-effect), we studied the incidence of WNV infection in relation to meteorological data recorded during the 8 weeks prior to the diagnosis. Therefore, we implemented a conditional Poisson regression in the context of lag-distributed models, which are suitable to explore the delayed effect of an exposure. Specifically, we used distributed lag non-linear models (DNLM), two-dimensional models developed to explore exposure-lag-response relationships along both the dimensions of exposure and lag (Gasparrini et al. 2010; Imai et al. 2015). These models use a cross-basis function, derived through a special tensor product of two independent functions, in order to analyze the exposure-response relationship and lag-response effect jointly. In our study, the effect of climatic parameters was modelled with a linear function, while the lag effect was modelled through a cubic basis spline with 4 degrees of freedom (df). The selection of the proper spline function for the lag-effect was based on the Akaike Information Criterion (AIC). We began the distributed lag models at lag 1 (the week before the week of diagnosis), hypothesizing that, since that WNV incubation period lasts 0-7 days (Rudolph et al. 2014), the risk should be null at lag 0 (week of diagnosis). The estimates can be plotted using a three-dimensional graph to show the Incidence Rate Ratio (IRR) along both exposure and lag dimension. Since the effect of climatic parameters was modelled as linear we estimated, for each lag, the IRR for an increase of 1 °C for the weekly average of minimum, mean and maximum temperatures and an increase of 5mm for the weekly total precipitation. The lag-specific IRR was derived by exponentiating the estimated regression coefficient, namely the variation in log-rate, for a unit increase of each climatic parameter for all specific lag (lag 1-8). In addition, we estimated the overall cumulative effect, that is the sum of each specific lag contribution over the whole lag period and can be interpreted as the overall risk. To control further for residual seasonal confounding, we included a cubic basis spline function with 5 df of the week number of the year, able to capture the seasonal pattern of the case distribution observed during the transmission period.

In addition, during summer holidays people are more likely to move out from their area of residence for leisure reasons. Thus, change of geographical location between the case and the control period would violate an assumption of the case-crossover design and possibly introduce bias. The potential impact of this source of bias was assessed in a sensitivity analysis in which we adjusted for holiday periods, defined as the two weeks around the 15th of August.

The software used to compute analysis is R, version 3.5.0 (R Development Core Team 2018). The packages used for statistical analysis are “splines” “dlnm” and “gnm”.

3. Results

In total, 213 cases were diagnosed during the study period in Northern Italy and included in the case-crossover analysis. During 2010-2015 period, 25 provinces of Northern Italy out of 42 (60%) reported human cases of WNV infection. Figure 1 shows the average of crude incidences of WNV infection per 1,000,000 inhabitants in each province over the 6-year period. Distribution of cases by week of the year (Fig 2) shows that the WNV infection has a seasonal pattern in Italy, with all cases being notified during the summer/autumn period. All human cases occurred between the 28th and 44thweek of the year with a peak at the end of August (36th week). This pattern has suggested the inclusion of the spline function of time to further adjust seasonal confounding.

Results, both crude and adjusted for seasonality, conducted on climatic parameters recorded up to 8 weeks prior to the diagnosis in relation to the risk of WNV infection are shown in Figure 3 and Table 1. The three-dimensional plots, show the entire surface of the adjusted IRRs in relation to maximum temperatures/precipitation at all lags considered (Figure 3a). Figure 3b shows the estimated effect of a unit increase in maximum temperatures and precipitation over the 8-week lag (continuous line: adjusted IRR, dashed line: crude IRR). Crude and adjusted lag-specific estimates for a unit increase in temperatures/precipitation are reported in Table 1. We found that the weekly average of maximum temperatures might affect the risk of WNV infection after 5 and 6 weeks (Fig 3). As shown in Table 1, the highest effect on WNV incidence was observed considering maximum temperatures recorded in the 6th week prior to diagnosis (adjusted IRR for 1°C increase in maximum temperatures at lag 6: 1.11; 95% CI 1.01-1.20). However, we did not find evidence of a positive overall cumulative effect for 1°C increase in maximum temperatures on WNV infection risk in the following weeks (Table 1). Weekly average of mean and minimum temperatures was not associated with the risk of WNV infection at any lag (Table 1). Weekly total precipitation recorded at lag 1-4 resulted positively associated with the risk of WNV infection (Fig 2b). As reported in Table 1, the maximum effect of precipitation was found with the precipitation recorded two weeks before diagnosis (lag 2) (adjusted IRR for 5 mm increase of weekly total precipitation at lag 2: 1.16; 95% CI 1.08-1.25). We found that 5 mm increase in weekly total precipitation was associated with a positive overall cumulative effect in the following 8 weeks: adjusted overall risk of 1.62 (95% CI 1.03-2.56). Lastly, when we adjusted for summer holidays in sensitivity analyses results were not affected more than marginally (results not shown).

Table 1

Risk of WNV infection in relation to unit increase[a] in temperature and precipitation.

1°C increase in weekly average of maximum temperature				
Lag (Weeks)	IRR1[b]	95% CI	IRR2	95% CI
1	0.95	0.88-1.03	0.91	0.81-1.01
2	1.00	0.95-1.03	0.93	0.83-1.04
3	1.04	1.00-1.09	0.98	0.88-1.10
4	1.09	1.05-1.14	1.04	0.95-1.15
5	1.13	1.08-1.17	1.09	1.00-1.19
6	1.13	1.08-1.18	1.11	1.01-1.20
7	1.09	1.04-1.14	1.06	0.98-1.15
8	0.99	0.91-1.08	0.94	0.84-1.04
Cumulative effect	1.48	1.22-1.80	1.03	0.56-1.87
1°C increase in weekly average of mean temperature				
Lag (Weeks)	IRR1	95% CI	IRR2	95% CI
1	0.95	0.86-1.05	0.88	0.77-1.01
2	1.00	0.96-1.04	0.90	0.79-1.03
3	1.05	1.00-1.11	0.95	0.83-1.09
4	1.10	1.05-1.15	1.02	0.90-1.15
5	1.13	1.08-1.18	1.08	0.97-1.20
6	1.13	1.08-1.19	1.09	0.99-1.21
7	1.09	1.03-1.15	1.04	0.94-1.15
8	1.00	0.91-1.12	0.91	0.79-1.04
Cumulative effect	1.53	1.23-1.92	0.86	0.41-1.80
1°C increase in weekly average of minimum temperature				
Lag (Weeks)	IRR1	95% CI	IRR2	95% CI
1	0.96	0.86-1.07	0.91	0.80-1.05
2	1.01	0.96-1.06	0.90	0.79-1.03
3	1.06	1.00-1.12	0.93	0.81-1.07
4	1.10	1.05-1.15	0.98	0.86-1.12
5	1.12	1.08-1.17	1.03	0.92-1.15
6	1.12	1.07-1.18	1.04	0.93-1.17
7	1.09	1.03-1.16	1.00	0.89-1.12
8	1.02	0.92-1.15	0.88	0.75-1.02
Cumulative effect	1.60	1.24-2.07	0.71	0.32-1.56
5 mm increase in weekly total precipitation				
Lag (Weeks)	IRR1	95% CI	IRR2	95% CI
1	1.02	0.97-1.08	1.12	1.06-1.20
2	1.05	1.00-1.10	1.16	1.08-1.25

3	1.03	0.98-1.09	1.15	1.06-1.24
4	1.00	0.95-1.05	1.10	1.02-1.19
5	0.95	0.90-1.01	1.04	0.97-1.12
6	0.92	0.87-0.97	0.99	0.92-1.07
7	0.91	0.86-0.96	0.97	0.90-1.03
8	0.94	0.88-0.99	0.98	0.92-1.05
Cumulative effect	0.82	0.57-1.14	1.62	1.03-2.56

[a] Estimates for a unit increase are derived by exponentiating the estimated regression coefficient, namely the variation in log-rate, for a unit increase of meteorological variables. Estimates for *n*-fold unit increase is obtainable by raising the estimate to the *n*-power

[b] IRR1: Crude Incidence Rate Ratio; IRR2: Incidence Rate Ratio adjusted for seasonality; CI: Confidence Interval

Figure 1

Average of crude incidences of WNV infection per 1,000,000 person-years in Italian provinces during the study period. Framed area corresponds to the study area.

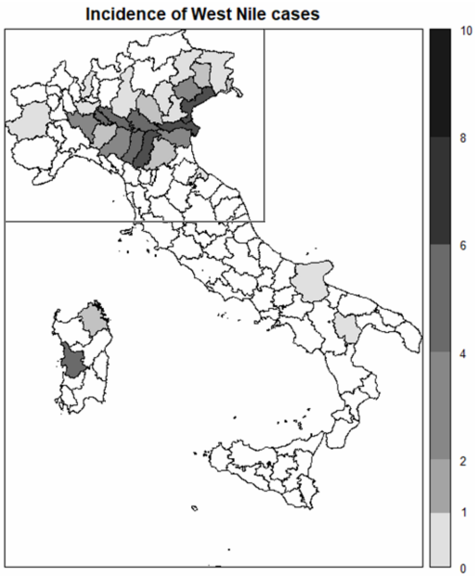


Figure 2

Total number of WNV infection cases observed in Northern Italy during the study period (2010-2015) by week *of* the year (left) and by week *and* year (right)

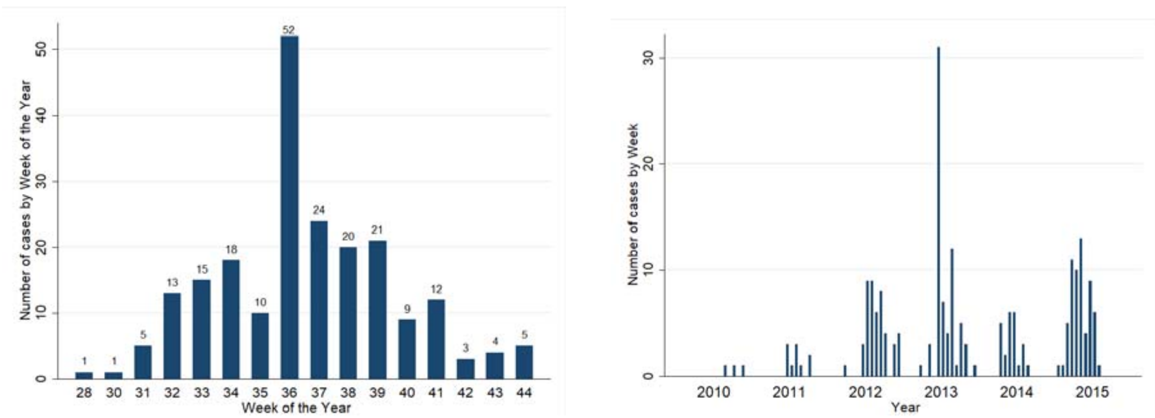


Figure 3

Fig. 3a (left) IRR2 (adjusted for seasonality) of WNV infection by weekly average of maximum temperatures (°C) and weekly total precipitation (mm), using a natural cubic spline–linear effect DLNM with 4 df basis cubic spline for lag and linear effect for exposure.

Fig. 3b (right) The estimated IRR2 (adjusted for seasonality) and 95% confidence intervals in unit increase of weekly average of maximum/minimum temperature (1 °C) and of weekly total precipitation (5mm) over 8 weeks of lag. Dashed line: IRR1 (not adjusted for seasonality)

Figure 3

Figure 3a

3D Graph of effect of Max T

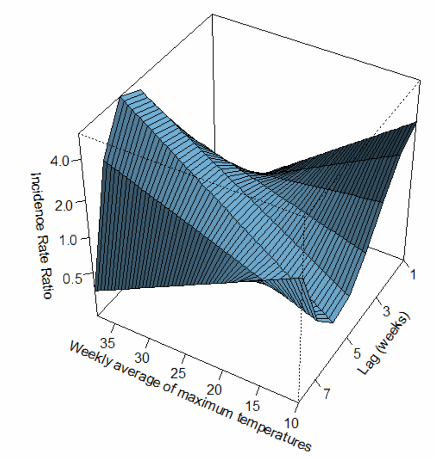
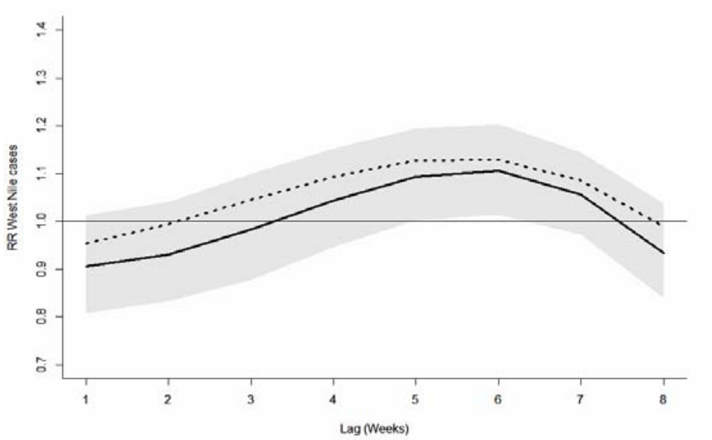
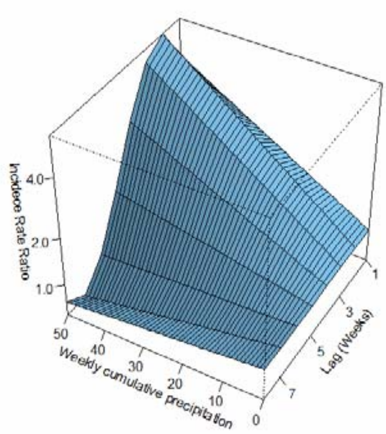


Figure 3b

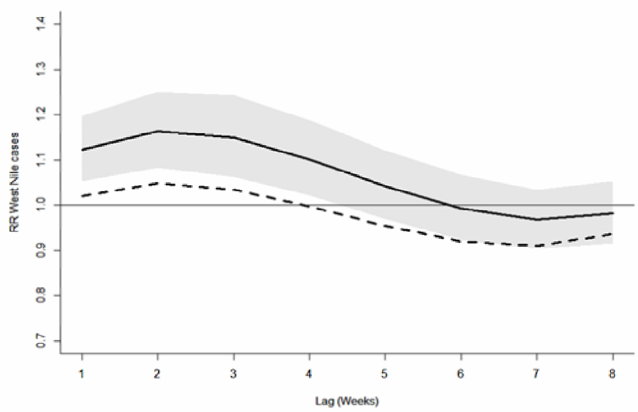
Lag effect of 1°C increase in weekly average of Max T



3D Graph of effect of Tot Prec



Lag effect of 5mm increase in weekly Tot Prec



4. Discussion

Our study revealed that cases in Northern Italy are notified between July and October, with a peak at the end of August. The transmission season is similar to the activity period (May-November) of mosquito *Culex Pipiens,* the main WNV vector in Italy (Bisanzio et al. 2011).

Our study is, to our knowledge, the first to assess the lag-effect of meteorological exposures and risk of WNV infection in Italy, including all incident cases diagnosed in Northern Italy between 2010 and 2015. Methodologically, the main strength of this study is the application of DLNMs in the context of a time stratified case-crossover design in order to explore delayed effects of exposures. We further included in the model a seasonal term (namely a spline function of time) to enhance the study validity, as it has been shown that in presence of a strong seasonal pattern of exposures and outcomes, time-stratified case-crossover studies might still be biased by residual seasonal confounding (Whitaker et al. 2007). Since we were interested in evaluating the short-term effect of the weekly variation of climatic parameters on the incidence of WNV infection from here onwards we will discuss only results adjusted for seasonality.

We found evidence of association, despite no overall cumulative effect, between maximum temperatures recorded in the 5^{th} and 6^{th} weeks prior to diagnosis (lags 5 and 6) and the incidence of WNV infection. Several studies have evaluated the effect of the temperatures on WNV ecology and transmission among mosquitoes, birds and humans in different areas worldwide (Gubler 2007; Paz 2015a; Paz and Semenza 2013), and many of them showed that temperatures may play an important role in the virus transmission cycle. However, only few studies have assessed the risk of WNV infection in humans in relation to temperatures with the specific aim of evaluating the lag effect. One correlation study conducted in Israel, Greece, Romania and Russia analyzed human cases of WNV infection notified during the

summer of 2010 in relation to temperature anomalies, namely temperatures recorded in 2010 compared with the perennial weekly average of 1981–2010. This study found an association between WNV cases and temperature at lag 0-1 (weeks) in Israel and Greece and at lag 3-4 (weeks) in Romania and Russia (Paz et al. 2013). One US study, a bidirectional case-crossover, not adjusted for seasonality, analyzed all incident cases of WNV infection notified between 2001 and 2005 (n= 16.298) in relation to the temperatures recorded in the 4 previous weeks, finding associations of similar strength for each lag (0-4 weeks) (Nile et al. 2009).
The lag of 5-6 weeks observed in our study might be explained by the complexity of the host/pathogen ecology. However, our study was not designed to assess the underlying mechanisms through which temperatures and precipitation may affect WNV infection, thus we can only speculate on the effects of climate parameters on vector and virus ecology.
It has been observed that the air temperature can augment virus replication rate and lead to higher viremia level in mosquito population (Reisen et al. 2006). Higher temperatures have been also shown to impact the vector transmission rate, by shortening the extrinsic incubation period (namely "the time from ingestion of an infectious bloodmeal until a mosquito is capable of transmitting virus infection to a susceptible organism") (Reisen 1989, Reisen et al. 2006). In addition, elevated temperatures can cause an expansion of the absolute number of mosquitoes and affect their feeding behaviours (Bisanzio et al. 2011; Conte et al. 2015). Thus, higher temperatures are believed to first impact the virus transmission in the enzootic cycle among mosquitoes and birds (Kilpatrick et al. 2008; Reisen et al. 2006) and, second, to affect the expansion of the proportion of infective mosquitoes, on which depend the human infection. The aforementioned pathways intrinsically imply a latency of the effect that, in addition to an incubation period of 0-7 days of human infection (Rudolph et al. 2014), might explain the overall latency of 5-6 weeks observed between increased temperatures and higher incidence of WNV infection cases.
However, it is noteworthy that the whole lag pattern presents negative point estimates at lag 1-2 and that the overall cumulative effect estimate is close to zero. For these reasons we cannot exclude that our findings of association between increased maximum temperatures and incidence of WNV infection at lag 5-6 might be due to chance.

Our results revealed an association between WNV infection and total precipitation recorded between the 1 and 4 weeks prior the diagnosis (lag 1-4). Levels of precipitations are believed to affect the patterns and the transmission of WNV (Paz 2015). However, findings about the relationship between precipitation and incidence of WNV cases are contradictory. Some studies reported that above-average precipitation can lead to higher risk of WNV outbreaks by expanding mosquitoes (Di Sabatino et al. 2014; Nile et al. 2009). On the contrary, other studies found that drought periods can induce outbreaks favoring the bird-to-bird viral transmission by facilitating the concentration of avian species in the few existing pools (Shaman et al. 2005). It is plausible that the response to precipitation might change over different geographical areas, depending on the differences in the characteristics of the local environment and in the ecology of vectors (Shaman et al. 2002, Paz 2015). Our results of associations between WNV infection cases and increased precipitation at lag 1-4 (weeks) can be due to the close relationship between aquatic environment and mosquito proliferation. Intermediate stages of Culex mosquitoes, such as larvae, are water dependent, and therefore, precipitation might be important, especially in drought periods such as summer, to create and maintain water pools that are necessary for the development of mosquitoes. Accordingly, an observational study reported that the WNV outbreak recorded in 2010 in central Macedonia, Greece, was preceded by unusually precipitation (Danis at al 2011).

Our study has three main limitations. First, we had information on the week but not on the day of diagnosis. Thus, we could not date back the exposure history starting from the day of symptoms onset, but only from the week preceding the week of the diagnosis. However, our study aligns with most of environmental studies conducted on infectious diseases, as typically surveillance systems for communicable diseases notify cases on a weekly scale. Second, since we had no information about the municipality but only about the province of residence of the cases, we linked each case to the meteorological station of the capital of its province in order to obtain data on the corresponding environmental exposures. This linkage might have introduced some non-negligible degree of exposure misclassification. However, since in case-crossover analysis the same subject is used both as case and as its own control, misclassification is likely to be non-directional, which would likely lead to conservative estimates. Third, the reason of the diagnosis (asymptomatic subjects: WNV positive blood; symptomatic subjects: West Nile Fever or West Nile Neuroinvasive Disease) was not available at the individual level. Asymptomatic subjects, such as blood donors, can be diagnosed during the incubation period, and therefore the lag-effect of environmental exposures might be different between asymptomatic and symptomatic groups. However, WNV infection cases diagnosed among the blood donors represent a minority of cases identified through the surveillance system. For instance, only 13 out of 61 cases (21% of the total) observed in Italy in 2015 were blood donors (ISS, 2015).

5. Conclusions

In conclusion, our results suggest that high temperatures might be associated with the incidence of WNV infection after a lag of 5-6 weeks, while heavy precipitation after a lag of 2-3 weeks. These results strengthen the evidence that the WNV is a climate-sensitive disease in an area where the process of endemization has recently started and underline that climatic parameters might be useful for detecting areas and periods of the year potentially characterized by a higher incidence of WNV infection

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