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Does the weather play a role in the spread of pandemic influenza? A study of H1N1pdm09 infections in France during 2009–2010

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SUMMARY

Understanding patterns of influenza spread and persistence is crucial for pandemic preparedness. The H1N1pdm09 virus caused the first influenza pandemic of the 21st century which resulted in at least 18500 deaths. Based on laboratory-confirmed primary-care case reports we investigated the role of weather conditions and socio-demographic variables in its initial spread and subsequent presence in France. Our findings suggest that low relative humidity and high population density were determinants in shaping the early spread of the virus at the national level. Those conditions also favoured the persistence of viral presence throughout the first 33 weeks of the pandemic. Additionally this persistence was significantly favoured by low insolation. These results confirm the increasingly recognized role of humidity in influenza dynamics and underlie the concomitant effect of insolation. Therefore climatic factors should be taken into account when designing influenza control and prevention measures.

Key words: Influenza A, modelling, pandemic, spread of disease.

INTRODUCTION

Influenza is one of the most significant infectious diseases in humans, considered to be associated with about 250 000–500 000 deaths worldwide annually [1]. The economic burden of influenza is also particularly important, notably due to productivity decrease, treatment costs and hospitalizations. As an example, in the United States the total economic burden of influenza epidemics is estimated to reach US$87.1 billion annually [2]. In temperate regions, annual influenza dynamics follow a clear seasonal pattern marked by an infection peak during the winter months, while this seasonality is less defined in tropical areas, where infections occur throughout the year [3]. Episodically, new influenza variants, for which no previous immunity exists, invade the human population and cause pandemics. The three pandemics of the last century alone resulted in the deaths of >50 million people [4].

A growing number of studies suggest a link between seasonal influenza dynamics and particular weather conditions [5]. Low temperature, low humidity (either absolute or relative) and low insolation (defined as the

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amount of solar energy that reaches the earth's surface) have been associated with the onset and spread of influenza infection at different levels (see [6] for a review). As these factors can influence contact rates, immunity and virus survival in the environment, the mechanisms underlying these relationships need to be determined. To our knowledge, the only studies focusing on the role of climatic parameters on pandemic emergence and dynamics during the 20th century investigated the influence of El Nino events (ENSO). Strong or prolonged ENSO cold phase appeared to favour influenza pandemics [7]. ENSO cold phases have also been linked to increased seasonal influenza mortality and morbidity in France and the USA [8].

The last pandemic was due to a novel avian/swine/human reassortant that was first detected in Mexico in March 2009. This new variant rapidly spread worldwide, notably thanks to the intense air traffic existing between Mexico and a number of big cities in other continents [9]. A year later, 214 countries and overseas territories had reported cases of pandemic influenza H1N1 2009 including 18 500 laboratory-confirmed associated deaths [10]. According to extrapolations based on a modelling approach, more than 280 000 deaths may have been associated with the H1N1 pandemic worldwide from April 2009 to August 2010 [11]. Yet, in most countries (including France), the burden of the pandemic was mild compared to what is generally observed during seasonal epidemics in terms of both mortality and morbidity [12]. Interestingly, the peak of pandemic activity occurred during similar climatic seasons in each country, whatever the first detection date of the new variant. For instance, this peak took place during the autumn/winter period in most temperate countries while no clear seasonal pattern emerged in tropical and subtropical countries [13]. In the same way at a smaller scale, within Brazil, which encompasses several climatic zones, there was a marked spatial structure of the period of peak activity. In the southern temperate region, the peak activity occurred during winter while in the northern equatorial area it took place during the rainy season [14]. Thus the timing and the burden of the pandemic appeared to be at least partly driven by climatic factors.

A few studies addressed the relationship between different weather conditions and the course of the pandemic at different levels (Table 1; [5, 15–22]). Here we aimed at discovering, at the national level, the impact of climatic factors when socio-demographic drivers are accounted for, on the initial propagation of pandemic H1N1 as well as on the presence of this pandemic virus in different localities throughout the first months of the pandemic. We chose to investigate France, where 13–24% of the population was infected, as two complementary surveillance networks collected detailed data on influenza infections [23] in order to compare our results within this European temperate country with those obtained in other continents.

METHODS

Epidemiological data

We used presence/absence of influenza laboratory-confirmed cases reported by the GROG network during the 33 weeks (31 August 2009 to 18 April 2010) of active surveillance in 235 French cities, by 286 primary-care practitioners distributed throughout metropolitan France (Fig. 1). Each practitioner collected nasopharyngeal swabs from patients consulting for acute respiratory infections. The samples were sent to one of the two national reference centres for influenza viruses or another laboratory working with the GROG network to test if the observed infections were actually due to an influenza virus. If the presence of an influenza virus was confirmed, the strain involved was also determined (see [24] and http://www.grog.org/ for more details on diagnostic methods). The H1N1pdm09 virus was considered to be present in a city if at least one infection case was laboratory confirmed during the focus week in that place. The virus was considered to be absent if at least one sample had been collected in the city during the focus week and no positive sample had been observed. The city was not considered if no sample had been collected since absence of data could be due to other factors than absence of the virus.

Climatic and socio-demographic variables

We chose to study temperature, humidity and UV radiations because these parameters have been extensively linked with influenza transmission (see [6] for a review). We also included school schedules because it has been shown that school closures have a negative effect on influenza transmission in several countries including France [25]. We added demographic factors as a proxy of contact rate patterns as big cities are more likely to possess a concentration of places (hospitals, schools, etc.) and transport hubs (airports, train

Table 1. *Summary of the results of other studies addressing the influence of climatic factors on H1N1pdm09 transmission*

Ref.	Study area	Data	Temperature	Relative humidity	Absolute humidity	Solar radiation	Precipitation	Other
[15]	Chile	ILI	Negatively associated	Negatively associated	Negatively associated	n.a.	Negatively associated	
[16]	China	CC	Negatively associated	Negatively associated	n.a.	n.a.	No correlation	
[17]	12 European countries	CC	No correlation	No correlation	Negatively associated	n.a.	n.a.	Wind speed and pressure, no correlation
[18]	Canada	CC	Negatively associated	n.a.	Negatively associated	n.a.	n.a.	
[22]	Brisbane (Australia)	CC	Negatively associated	n.a.	n.a.	n.a.	Negatively associated	
[19]	Okinawa (Japan)	CC	Negatively associated	Negatively associated	n.a.	Negatively associated	Negatively associated	
[20]	Niamey (Niger)	CC	Negatively associated	No correlation	n.a.	n.a.	n.a.	Wind speed, no correlation, visibility positively associated
[5]	USA	ILI & CC	n.a.	n.a.	Negatively associated	n.a.	n.a.	
[21]	Changsha (China)	CC	Negatively associated	Negatively associated	Negatively associated	n.a.	n.a.	Wind speed negatively associated, pressure positively associated

ILI, Influenza-like illness cases; CC, confirmed cases; n.a., data not available.

stations, etc.) that favour both influenza amplification and its geographical spread.

When investigating the initial spread of the virus, we additionally considered the distance of each locality to the nearest of the four French cities where H1N1pdm09 was first reported by the GROG network members and to Paris, considered as the main national transport hub, to determine if the proximity to one of the original pandemic foci or to the capital city was correlated with early reports of H1N1 cases.

We used Meteo-France weekly climatic data including temperature (mean, maximum, minimum), relative humidity (mean, maximum, minimum) and mean insolation (see Table 2). Additionally, air pressure was used along with relative humidity and altitude to calculate mean absolute humidity following the formulae used in the conversion software available at http://www.cactus2000.de, and based on [26].

Each virological sampling site was associated with the nearest meteorological station that recorded temperature, humidity and air pressure. The mean distance between a sampling site and the associated meteorological station was 20·7 km (s.d. = 16·5 km) with a maximum of 74·0 km and a minimum of 1·3 km. Insolation data was added only when these stations also recorded this parameter (in 151 cities). Indeed, systematically searching for station recording insolation data would have greatly increased the mean distance between meteorological and epidemiological sampling sites, thus reducing the accuracy of climatic data. Thus two datasets were used in the statistical analyses: (i) the first (D1) contained all the cities for which virological data were available ($n = 235$), (ii) the second (D2) only included the 151 cities for which both virological and insolation data were available.

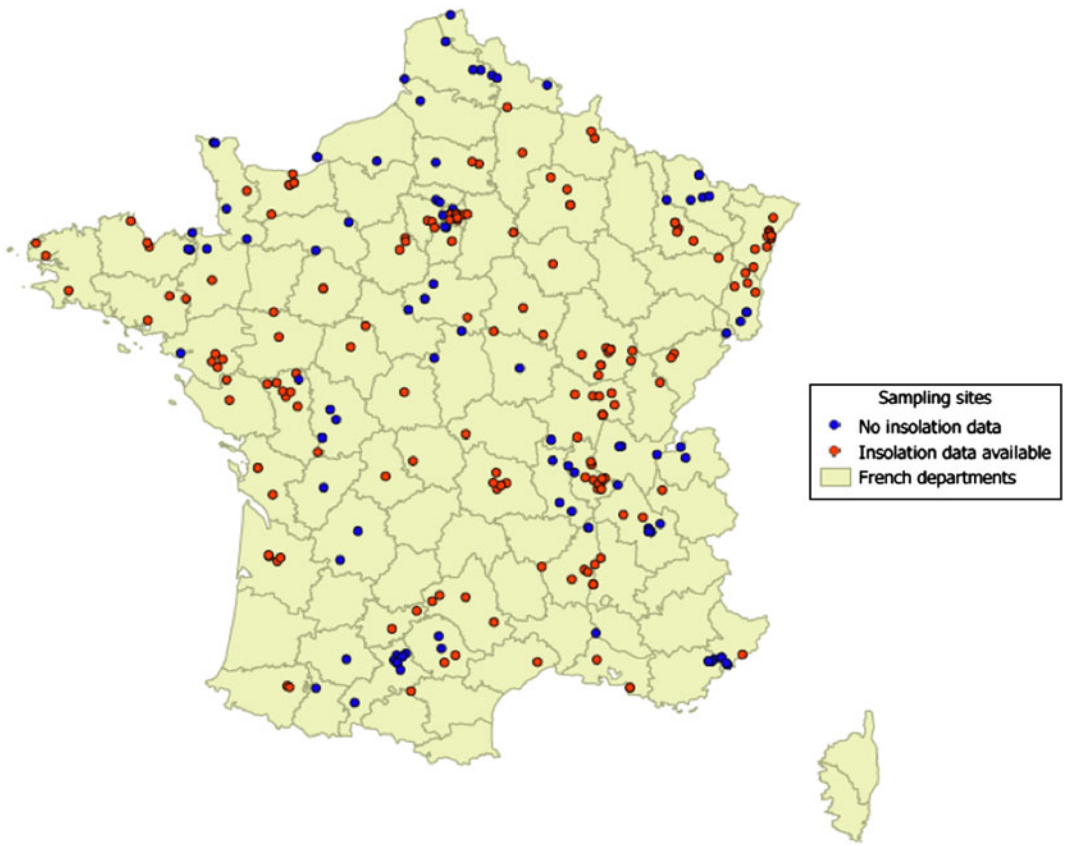

Fig. 1. Location of the 235 French cities studied. Cities for which insolation data were available are represented by red dots, others are shown as blue dots.

Population sizes and densities were included at the city level and the department level using the last data recorded by INSEE ([27]; Table 2). Finally, school schedules were obtained from the French Ministry of Education website (http://www.education.gouv.fr/cid197/les-archives-calendrier-scolaire-partir-1960.html; Table 2).

Statistical analysis

To test the spatial autocorrelation between epidemiological data we used two Mantel tests. The first one tested the correlation between the distance separating cities and the similarity of epidemiological data. The second tested the correlation between the distance separating cities and the date of the first case reported by the GROG network in each town.

To assess the impact of climatic and socio-demographic variables on the initial spread of the virus we used Generalized Linear Models (GLM). We tested the correlation between the early report of cases and these variables. The locality was considered to have experienced an early arrival of the virus if at least one confirmed case was reported during the first weeks of the French epidemics. Those tests were run using seven different intervals to define the period of early arrival from the first 2 weeks (31 August to 13 September 2009) to the first 8 weeks (31 August to 25 October 2009) after the first report of H1N1pdm09 infection in the country. For each period of time we first tested the correlation between the presence of the virus during this period and each variable in a univariate GLM model. We then selected the variables that had a significant effect in those models for each time period and included them in a multivariate GLM model. If the correlation between two significant variables was higher than 0·4 we chose only one of them. We used a backward selection process based on Akaike's Information Criterion (AIC) to select the best model for each time interval.

To investigate the role of climatic and socio-demographic variables on H1N1pdm09 presence throughout the first 33 weeks of the virus circulation in France we used Generalized Estimating Equations (GEEGLM function in R statistical software; http://www.r-project.org) models because they allowed us

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Table 2. *General statistics for all the variables we studied. General statistics are given for both datasets (D1, 235 cities; D2, 151 cities), except for insolation, which was available in 151 cities only*

	Mean		Median		Range	
Variable	D1	D2	D1	D2	D1	D2
Weekly minimum temperature (°C)	4·7	4·3	5·1	4·7	−8·4 to 19·1	−8·4 to 19·1
Weekly maximum temperature (°C)	12·4	11·9	12·4	11·9	−2·5 to 30·4	−2·3 to 30·4
Weekly average temperature (°C)	8·3	7·9	8·7	8·2	−5·2 to 24·1	−5·2 to 22·8
Weekly minimum relative humidity (%)	61·1	61·9	63·8	64·1	20·9 to 96·7	23 to 96·7
Weekly maximum relative humidity (%)	93·7	93·9	94·7	95·0	61·7 to 100·0	63·2 to 100·0
Weekly average relative humidity (%)	80·7	80·9	82·7	83·1	44·4 to 99·1	49·7 to 99·1
Weekly average absolute humidity (g/kg)	7·1	6·9	7·0	6·8	2·6 to 14·1	2·6 to 13·6
Weekly mean insolation (J/cm^2)	n.a.	675·2	n.a.	489·6	n.a.	91·3 to 2282·3
City population size 2008	56 698	72 131	10 883	9935	318 to 2 211 297	462 to 2 211 297
Department population 2008	846 313	833 717	710 034	647 420	123 907 to 2 564 969	123 907 to 2 564 969
City population density 2008 (pop./km^2)	1763·7	2009·2	652·2	595·7	15·8 to 25 192·7	15·8 to 25 192·7
Department population density 2008 (pop./km^2)	509·5	681·9	122·2	99·9	22·3 to 20 980·0	22·3 to 20 980·0
School holidays	**D1**: 5 weeks of holidays in 27 cities, 6 in 110 cities, and 7 in 98 cities		**D2**: 5 weeks of holidays in 19 cities, 6 in 65 cities and 7 in 67 cities		Considered as a binomial variable for each week in each city: 1 during school holidays; 0 during school time	

to model binomial data according to both quantitative and qualitative variables while taking into account their temporal autocorrelation through an autoregressive model of order 1 (AR-1). We first assessed the correlation between our variables using a pairwise correlation test. We then selected in each group of highly correlated variables the one that was the most significant while not being highly correlated with other groups of variables. Finally we used a backward step selection to select the best model.

RESULTS

Spatial autocorrelation

The correlation between the matrix of distances separating sampling sites and the week of detection of the first case was not significant (Mantel, 1000 iterations; $P = 0{\cdot}395$). In the same way, the correlation between the distance matrix and the matrix including all the virological presence/absence data was not significant (Mantel, 1000 iterations; $P = 0{\cdot}938$). Besides, the date of detection of the first influenza case was negatively correlated to both density and population size of city with density having the strongest effect, meaning that cases were detected earlier in the most densely populated cities (GLM: family Poisson, $\beta = -4{\cdot}70 \times 10^{-5}$, s.e. $= 9{\cdot}65 \times 10^{-6}$; $P < 10^{-5}$).

Initial spread of the virus

The effect of insolation, which was tested using the dataset containing the 151 cities for which insolation data were available, was not significant for any of the time periods considered in univariate GLM models. Thus we did not include this variable in multivariate models. The effect of all the other variables in univariate models was tested using the full dataset (containing 235 cities). Neither the distance to the nearest detected outbreak focus, nor the distance to Paris were significantly correlated with early viral presence in any time interval (i.e. first 2–8 weeks of the pandemic). Within the climatic variables mean relative humidity was negatively associated with early presence of H1N1pdm09 during each period considered except the longest one, the importance of this effect varied across the other time intervals (see Table 3). Conversely, no effect of the temperature was observed. Moreover, population density was consistently found to be positively associated with early viral presence in all intervals. In other words H1N1pdm09 viruses were more likely to be reported during the early detection period in the most densely populated cities than in the less densely populated cities whatever the time interval considered to define the period (2–8 weeks after the first case was reported by the GROG

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Table 3. *Effect of mean relative humidity and city population density on H1N1pdm09 case presence in 235 cities during each period considered in a bivariate model (with no interaction)*

	Mean relative humidity during the period		City density 2008	
Time period	β (S.E.)	P value	β (S.E.)	P value
31 Aug. to 13 Sept. 2009	$-4{\cdot}50\times10^{-2}$ ($3{\cdot}98\times10^{-2}$)	$4{\cdot}60\times10^{-2}$	$1{\cdot}09\times10^{-4}$ ($5{\cdot}46\times10^{-5}$)	$2{\cdot}60\times10^{-1}$
31 Aug. to 20 Sept. 2009	$-8{\cdot}54\times10^{-2}$ ($4{\cdot}37\times10^{-2}$)	$5{\cdot}10\times10^{-2}$	$1{\cdot}68\times10^{-4}$ ($5{\cdot}86\times10^{-5}$)	$4{\cdot}20\times10^{-3}$
31 Aug. to 27 Sept. 2009	$-8{\cdot}17\times10^{-2}$ ($4{\cdot}36\times10^{-2}$)	$6{\cdot}10\times10^{-2}$	$2{\cdot}09\times10^{-4}$ ($6{\cdot}53\times10^{-5}$)	$1{\cdot}40\times10^{-3}$
31 Aug. to 4 Oct. 2009	$-1{\cdot}20\times10^{-1}$ ($4{\cdot}00\times10^{-2}$)	$2{\cdot}60\times10^{-3}$	$1{\cdot}59\times10^{-4}$ ($5{\cdot}98\times10^{-5}$)	$7{\cdot}80\times10^{-3}$
31 Aug. to 11 Oct. 2009	$-9{\cdot}47\times10^{-2}$ ($3{\cdot}89\times10^{-2}$)	$1{\cdot}50\times10^{-2}$	$1{\cdot}51\times10^{-4}$ ($5{\cdot}62\times10^{-5}$)	$7{\cdot}20\times10^{-3}$
31 Aug. to 18 Oct. 2009	$-7{\cdot}39\times10^{-2}$ ($3{\cdot}20\times10^{-2}$)	$2{\cdot}10\times10^{-2}$	$1{\cdot}75\times10^{-4}$ ($6{\cdot}02\times10^{-5}$)	$3{\cdot}70\times10^{-3}$
31 Aug. to 25 Oct. 2009	$-3{\cdot}13\times10^{-2}$ ($2{\cdot}97\times10^{-2}$)	$2{\cdot}90\times10^{-1}$	$1{\cdot}99\times10^{-4}$ ($6{\cdot}55\times10^{-5}$)	$2{\cdot}40\times10^{-3}$

Coefficient estimates (β) are given with their standard error (S.E.).

Table 4. *Effect of each variable on H1N1pdm09 case presence in a univariate model. The parameters and P values of univariate models are given for both datasets (D1, 235 cities; D2, 151 cities), except for insolation, which was available in 151 cities only*

	Effect in a univariate model (GEEGLM AR-1 correlation structure)			
	β (S.E.)		P value	
Variable	D1	D2	D1	D2
Weekly minimum temperature	$-1{\cdot}22\times10^{-2}$ ($7{\cdot}17\times10^{-3}$)	$-7{\cdot}42\times10^{-3}$ ($9{\cdot}40\times10^{-3}$)	$8{\cdot}80\times10^{-2}$	$4{\cdot}30\times10^{-1}$
Weekly maximum temperature	$-2{\cdot}60\times10^{-2}$ ($5{\cdot}87\times10^{-3}$)	$-1{\cdot}99\times10^{-2}$ ($7{\cdot}46\times10^{-3}$)	$9{\cdot}3\times10^{-6}$	$7{\cdot}70\times10^{-3}$
Weekly average temperature	$-2{\cdot}19\times10^{-2}$ ($6{\cdot}72\times10^{-3}$)	$-1{\cdot}58\times10^{-2}$ ($8{\cdot}62\times10^{-3}$)	$1{\cdot}10\times10^{-3}$	$6{\cdot}70\times10^{-2}$
Weekly minimum relative humidity	$2{\cdot}60\times10^{-2}$ ($2{\cdot}80\times10^{-3}$)	$3{\cdot}05\times10^{-2}$ ($3{\cdot}37\times10^{-3}$)	$<2\times10^{-16}$	$<2\times10^{-16}$
Weekly maximum relative humidity	$2{\cdot}29\times10^{-2}$ ($7{\cdot}16\times10^{-3}$)	$3{\cdot}41\times10^{-2}$ ($9{\cdot}24\times10^{-3}$)	$1{\cdot}40\times10^{-3}$	$2{\cdot}2\times10^{-4}$
Weekly average relative humidity	$3{\cdot}37\times10^{-2}$ ($4{\cdot}10\times10^{-3}$)	$4{\cdot}16\times10^{-2}$ ($5{\cdot}05\times10^{-3}$)	$2{\cdot}2\times10^{-16}$	$2{\cdot}2\times10^{-16}$
Weekly average absolute humidity	$-2{\cdot}83\times10^{-2}$ ($1{\cdot}52\times10^{-2}$)	$-8{\cdot}49\times10^{-3}$ ($1{\cdot}99\times10^{-2}$)	$6{\cdot}20\times10^{-2}$	$6{\cdot}70\times10^{-1}$
Weekly mean insolation	n.a.	$-2{\cdot}39\times10^{-3}$ ($1{\cdot}92\times10^{-4}$)	n.a.	$<2\times10^{-16}$
City population size 2008	$3{\cdot}71\times10^{-7}$ ($6{\cdot}12\times10^{-8}$)	$3{\cdot}58\times10^{-7}$ ($5{\cdot}03\times10^{-8}$)	$1{\cdot}40\times10^{-9}$	10^{-12}
Department population 2008	$1{\cdot}64\times10^{-7}$ ($7{\cdot}84{\cdot}10^{-8}$)	$1{\cdot}43\times10^{-7}$ ($1{\cdot}15\times10^{-7}$)	$3{\cdot}60\times10^{-2}$	$2{\cdot}10\times10^{-1}$
City population density 2008	$3{\cdot}28\times10^{-5}$ ($1{\cdot}68{\cdot}10^{-8}$)	$3{\cdot}79\times10^{-5}$ ($1{\cdot}77\times10^{-5}$)	$5{\cdot}10\times10^{-2}$	$3{\cdot}2\times10^{-2}$
Department population density 2008	$2{\cdot}85\times10^{-5}$ ($1{\cdot}40{\cdot}10^{-5}$)	$3{\cdot}39\times10^{-5}$ ($1{\cdot}25\times10^{-5}$)	$4{\cdot}10\times10^{-2}$	7×10^{-3}
School holidays	$3{\cdot}02\times10^{-2}$ ($0{\cdot}104$)	$1{\cdot}64\times10^{-1}$ ($1{\cdot}27\times10^{-1}$)	$7{\cdot}70\times10^{-1}$	$2{\cdot}00\times10^{-1}$

Coefficient estimates (β) are given with their standard error (S.E.).

network). The size of the city was also involved in similar positive associations in univariate models but we did not include it in multivariate models since population size and density were highly correlated. School schedules were not included in this analysis since they did not differ between cities during the first 8 weeks of the pandemic. The best multivariate models selected for each time period were similar and contained mean relative humidity and population density, the effects of both variables are presented in Table 3. Thus, our analyses showed that low relative humidity and high population density were favourable to the early presence of H1N1pdm09 in French cities.

Presence of H1N1pdm09 throughout the first 33 weeks of the pandemic

Correlations between the different variables ranged from 0·05 to 1. We selected one variable in each group of highly correlated variables, based on the significance of its effect on viral presence within an univariate GEE model with AR-1 correlation structure (see Table 4). Correlations between the variables

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we selected were $\leqslant 0{\cdot}4$. The values that are presented in Table 2 were obtained using the dataset containing insolation values (D2, 151 cities). For comparison purposes univariate GEE models with AR-1 correlation structure were also used to select variables using the complete dataset (D1, 235 cities) and excluding the insolation variable. The same variables were selected using D1 and D2 (except insolation that could not be included using D1). Therefore all further steps of our analysis were done on the dataset containing insolation values (D2) since insolation had a highly significant effect on H1N1pdm09 presence.

We used a backward selection process to select the model that best fitted our data. The selected model as well as corresponding parameters are presented in Table 5. According to that model, both insolation and relative humidity had a negative effect on pandemic influenza cases. Temperature also had a significant negative effect on case occurrence in a univariate model but could not be included since temperature and humidity are highly correlated. The population size of the cities had a positive effect on pandemic influenza cases. H1N1pdm09 infections were more likely to be observed during school time and the impact of meteorological conditions was less pronounced during school holidays. Finally, the highly significant temporal autocorrelation observed ($\alpha = 0{\cdot}327$, s.e. $= 0{\cdot}178$) showed that infections were more likely to occur in a city if cases had been observed there during the previous weeks.

DISCUSSION

Initial spread

At the European level the pandemic virus spread from West to East. This pattern was associated with the frequency of air travel from USA and Mexico and the different school calendars. Indeed the probability of observing an early first epidemic wave was higher in countries where schools were open when the first American cases were reported and where the connectedness with the first affected countries through air traffic was important [28]. At the national level our results did not highlight any correlation between the distance to the first detected foci of infection or to Paris and the early circulation of H1N1pdm09 in French cities. However, the largest cities with the highest population densities were more likely to report early cases. This finding is in accordance with observations made in the USA, where seasonal influenza infections seem to be synchronized in highly populated states and then spread to neighbouring states that have a smaller population [29]. In France a recently published spatial analysis of pandemic H1N1 spread showed, based on influenza-like illness cases, that three successive phases were observed. First, cases were simultaneously detected in Paris and several regions highly connected with the capital, the virus then quickly spread to all large cities and finally to rural areas around these cities [30]. Our results, based on laboratory-confirmed cases, appear consistent with this pattern as we highlighted that cases were more likely to occur in the most densely populated areas (i.e. the major conurbations). Moreover, our findings are in line with the conclusion of a previous study on the spread of seasonal influenza in France, which showed that distance between regions had no effect on viral spread contrary to different types of transport flows (road, train, air traffic; [31]).

According to these results, we suggest that French regions are highly interconnected, which abolishes any distance effect in viral spread between cities at the national level. This connectedness is higher in large cities, which could explain why pandemic influenza was more likely to be present in such cities and reach them earlier, in the same way that seasonal influenza first reaches states with a large population in USA [29]. Yet, alternatively, the simultaneous arrival of virus observed in several large French cities may have been associated with independent introductions from abroad and subsequent independent viral persistence in large cities. Phylogenetic studies of the strains isolated during the first weeks of the pandemic would be necessary to disentangle the role of local dynamics and connectedness between cities in shaping the initial spread of H1N1pdm09 in France.

Interestingly, our findings also highlight the role played by relative humidity during this first phase of the pandemic. Indeed they suggest that low relative humidity was favourable to the early spread of H1N1pdm09 in French cities. This represent the first evidence of a clear role of weather conditions on the spread of pandemic influenza at the European temperate country level.

Presence of H1N1pdm09 throughout the first months of the pandemic

We underlined a negative correlation between relative humidity and presence of H1N1pdm09 throughout the 33 weeks studied. In addition, during this period insolation was also negatively associated with the presence of pandemic virus. The effects of humidity

Table 5. *Results of the generalized estimating equations model of variables associated with pandemic influenza presence in 151 French cities. In both interactions the periods when children are at school are considered to be the reference state*

Variable	β (S.E.)	Wald	*P* value
Weekly maximum relative humidity	$-2{\cdot}26 \times 10^{-2}$ $(1{\cdot}28 \times 10^{-2})$	3·09	$7{\cdot}89 \times 10^{-2}$
Weekly mean insolation	$-2{\cdot}69 \times 10^{-3}$ $(2{\cdot}32 \times 10^{-4})$	134·48	$<2 \times 10^{-16}$
City population size 2008	$4{\cdot}71 \times 10^{-7}$ $(1{\cdot}32 \times 10^{-7})$	12·73	$3{\cdot}60 \times 10^{-4}$
School holidays	$-14{\cdot}6$ (4·04)	13·08	$3{\cdot}00 \times 10^{-4}$
Weekly maximum relative humidity/school holidays	$1{\cdot}46 \times 10^{-1}$ $(4{\cdot}15 \times 10^{-2})$	12·35	$4{\cdot}40 \times 10^{-4}$
Weekly mean insolation/school holidays	$1{\cdot}46 \times 10^{-3}$ $(4{\cdot}13 \times 10^{-4})$	12·55	$4{\cdot}00 \times 10^{-4}$

Coefficient estimates (β) are given with their standard error (S.E.).

and insolation we highlighted are in accordance with the results of experimental transmission studies as well as viral persistence studies. Indeed, human influenza A virus survival in the environment is favoured by low humidity, low temperature and low insolation [32]. Additionally, experimental transmission studies on mammals [guinea pigs (*Cavia porcellus*) and ferrets (*Mustela putorius*)] have shown that these conditions also favoured aerial transmission [33, 34]. A recent study confirmed that experimental transmission of H1N1pdm09 between guinea pigs was also favoured by low humidity and low temperature [35].

A similar impact of temperature and humidity on H1N1pdm09 spread has been highlighted in several countries and at various levels (see Table 1). Depending on the study, either absolute or relative humidity was shown to be significantly associated with occurrence of influenza cases. Here we confirm that temperature and humidity were also determinants in the persistence of H1N1pdm09 at the European country level. Moreover, we point out the potentially crucial role of insolation that has rarely been investigated thus far but has been shown to be negatively related with H1N1 occurrence in Niamey [20] and suggested to have a major role in shaping influenza epidemic seasonality worldwide [36].

However, further experimental transmission studies are needed to determine which mechanisms underlie the effects we evidenced. Indeed, weather conditions may affect influenza infections through multiple ways (see [37] for a review). First, they can favour viral survival in the environment as discussed above. Second, they can influence host susceptibility to the infection. For example, a prolonged under-exposure to UV radiations decreases the levels of vitamin D in the organism, which impairs immunity [38]. Third, weather conditions can influence contact rates between hosts and time spent indoors [39].

Limitations and soundness of our study

Our study was limited by the sampling protocol we used. Indeed, the sampling was performed in the cities where the GROG network members work with patients who had decided to consult their physician and that presented characteristic symptoms, which did not allow detection of asymptomatic cases. However, this limit is common to most studies based on epidemiological data. Furthermore, we decided not to include case number estimations in our analysis, since those that are collected in France by the Sentinel network are based on 'influenza-like case' numbers rather than on laboratory-confirmed cases which do not allow distinguishing influenza infections from other respiratory infections. This point appears especially important with the knowledge that some pathogens that can cause influenza-like symptoms, such as rhinovirus, were circulating in France before the beginning of the H1N1pdm09 pandemic and are thought to have influenced its timing [40]. Thus our analyses are based on less complete but more robust data compared to those that use influenza-like cases. Finally, our results are based on the correlation between climatic factors and the detection of influenza virus infections. Considering that correlation is not always due to a direct causal link, further experimental studies are needed to improve our understanding of the mechanisms underlying the association between particular meteorological conditions and the observation of influenza virus infections.

Perspectives

Improving the sampling protocol described above appears difficult since virological analyses are limited by their cost as well as by the supplementary workload associated with sample collection and shipment that is acceptable for the GROG network practitioners, while their workload is generally already high. Influenza surveillance needs to be urgently improved at the global level, since influenza virus spreads extremely rapidly from one country to another. In the European Union a network supervised by the ECDC is responsible for gathering national data (EISN). Yet the virological data collected by EISN are aggregated at the national level, thus they allow a comparison of viral dynamics across European countries but not within them. Moreover, the local data gathered by EISN are based on influenza-like illness (ILI) case detection. ILI cases are detected through the observation of symptoms that can be caused by different respiratory pathogens. Thus, to improve the efficiency of the European surveillance of influenza epidemics and pandemics such data should be supplemented in each country by virological data collected at the local level.

This need of surveillance appears especially acute if we consider that global changes will potentially exacerbate the explosive nature of influenza pandemics. Indeed, the intensification of livestock production coupled with an exponential increase of goods and people flows create new opportunities for new viral variants to emerge and spread. Further, as highlighted by our results, weather conditions seem to influence pandemic influenza dynamics along with population density and school schedules, which means that climatic changes may have important impacts on future pandemics. To understand these future impacts and meet the challenge of pandemic influenza prevention in a changing world, the mechanisms underlying the role of weather conditions and, more generally, of environmental conditions, on influenza dynamics should be investigated. Experimental infection studies exploring the mechanisms involved in influenza virus transmission are notably needed to build up relevant models that could help setting up timely prevention and control measures.

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DECLARATION OF INTEREST

None.

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