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Different transmission patterns in the early stages of the influenza A(H1N1)v pandemic: A comparative analysis of 12 European countries[☆]

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ABSTRACT

Following the emergence of a novel strain of influenza A(H1N1) in Mexico and the United States in April 2009, its epidemiology in Europe during the summer was limited to sporadic and localised outbreaks. Only the United Kingdom experienced widespread transmission declining with school holidays in late July. Using statistical modelling where applicable we explored the following causes that could explain this surprising difference in transmission dynamics: extinction by chance, differences in the susceptibility profile, age distribution of the imported cases, differences in contact patterns, mitigation strategies, school holidays and weather patterns. No single factor was able to explain the differences sufficiently. Hence an additive mixed model was used to model the country-specific weekly estimates of the effective reproductive number using the extinction probability, school holidays and weather patterns as explanatory variables. The average extinction probability, its trend and the trend in absolute humidity were found to be significantly negatively correlated with the effective reproduction number – although they could only explain about 3% of the variability in the model. By comparing the initial epidemiology of influenza A (H1N1) across different European countries, our analysis was able to uncover a possible role for the timing of importations (extinction probability), mixing patterns and the absolute humidity as underlying factors. However, much uncertainty remains. With better information on the role of these epidemiological factors, the control of influenza could be improved.

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Introduction

A novel strain of influenza A H1N1 (A(H1N1)v) was first identified in Mexico and the Southern United States in April 2009. The virus rapidly spread to Europe being first identified in Spain and the United Kingdom (UK) on 27th April (Health Protection Agency et al., 2009; Sierra Moros et al., 2010). Other countries in Europe (particularly those with frequent flight connections to Mexico and the US) started confirming cases shortly afterwards (Belgian working group on influenza A(H1N1)v, 2009; Gilsdorf et al., 2009; Hahné et al., 2009; Health Protection Agency et al., 2009; New influenza A(H1N1) investigation teams, 2009; Surveillance Group for New Influenza A (H1N1) Virus Investigation and Control in Spain, 2009; Surveillance Group for New Influenza A(H1N1) Virus Investigation in Italy, 2009). The epidemiology in Europe in the late spring and summer was typified by sporadic cases and isolated self-limiting outbreaks linked to importations (see Fig. 1), with one apparent exception. A major generalised epidemic of A(H1N1)v occurred in the UK in June and July which only declined once schools closed for the summer holidays at the end of July (Baguelin et al., 2010; Miller et al., 2010). No such major epidemic was reported elsewhere in Europe until the autumn, during which time the UK had its second wave of infection. Whilst one would expect an influenza variant to have a rather similar transmission potential in these countries we show that the observed epidemiology suggests a much higher transmissibility (measured by the average number of secondary cases per case) of A(H1N1)v during summer 2009 in England than elsewhere in Europe. We then explore a series of epidemiological hypotheses that might explain the differences. First, these could be explained by chance: i.e. that the

epidemiological parameters were similar across countries but the epidemic took off in England and not in other countries by chance. Second, the difference could be explained by a difference in the susceptibility profile. Third, the difference could be explained by a difference in the age distribution of imported cases. Fourth, differences in contact patterns could have favoured the spread in age groups which mix with the more susceptible age groups. Fifth, the difference could be explained by a difference in implemented control measures. Sixth, the difference could be explained by a late school closure relative to the time of the introduction in the UK. Seventh, the weather patterns (pressure, relative and absolute humidity, temperature, and wind speed) might have played an influential role. This paper aims to test these hypotheses against available data from 12 European countries. In order to do so, we analyse data on the time of symptom onset of confirmed cases over a period from April 2009 to October 2009, and data on the control measures that were implemented, school holidays, and weather. This analysis of transmission patterns of A(H1N1)v during the early phase of infection in Europe helps to build a better understanding of how influenza spreads and what factors may have influenced the different epidemiological patterns observed.

Materials and methods

Reported cases

In each of the 12 countries (Belgium, Bulgaria, England, France, Germany, Italy, Luxembourg, Netherlands, Portugal, Romania, Slovakia, and Spain) data were collected on laboratory confirmed A(H1N1)v

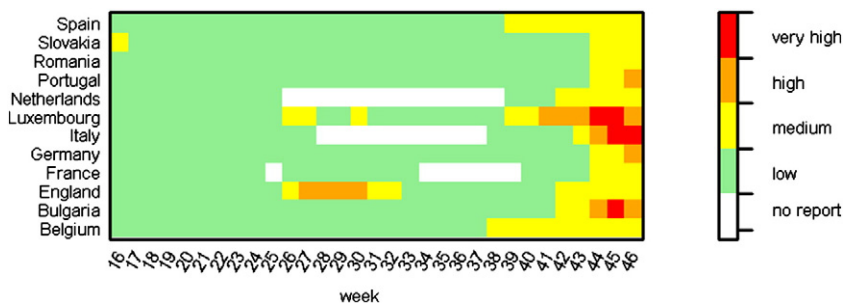


Fig. 1. The intensity of clinical influenza like illness and acute respiratory infection activity in 2009 as reported by the European Influenza Surveillance Network. In most countries A(H1N1)v was found to be the dominant type during this period. Low intensity here reflects no influenza activity or influenza activity at baseline level, medium: level of influenza activity usually seen when influenza virus is circulating in the country based on historical data, high: higher than usual influenza activity compared to historical data and very high: influenza activity is particularly severe compared to historical data.

cases. The country-specific study period was defined by the period between the occurrence of the first case of novel A(H1N1)v influenza and the end of testing the vast majority of (ideally all) suspected cases (as determined by local experts' opinion, which in most countries corresponded to the date of change in policy from the recommendation to test all cases (Health Protection Agency; Influenza A(H1N1)v investigation teams et al., 2009; Italian Ministry of Health; Ministero Da Daude; Santa-Olalla Peralta et al., 2010; Sierra Moros et al., 2010)) or the reopening of schools after summer holidays if this occurred earlier. In respect to the case definition (Table S1) a confirmed case was defined as having a positive laboratory test by reverse transcription polymerase chain reaction (RT-PCR), viral culture or showing a four-fold rise in influenza A(H1N1)v specific neutralising antibody titre from a convalescent (generally collected 3–4 weeks after onset of illness) to an acute sample (collected within 1 week after symptom onset in the same individual). A suspected case was defined as someone who fulfilled the country-specific epidemiological and clinical criteria but was not tested at the time of data collection for this analysis (England 29/07/2009, France 20/10/2009, all suspected cases were tested in the other countries).

Data on confirmed cases were used including information on: date of reporting, date of illness onset, travel to an at-risk country within the last 7 days prior to illness onset, gender and age where available. In the UK only data from England were available for this analysis, although Scotland, Northern Ireland and Wales had similar epidemic patterns in the summer of 2009 (Communicable Disease Surveillance Centre Northern Ireland; Health Protection Scotland; National Public Health Service for Wales).

Due to the absence of any data on the date of illness onset in Luxembourg we assumed the reporting delay to be either zero or 1 day (equally likely). For all other countries the country-specific reporting-delay distribution was obtained by fitting a gamma distribution to the observed data (Figure S1) and this was used for imputing the date of illness onset for cases with only data available on the date of report: for the calculation of the effective reproduction number (the number of secondary cases generated by an average primary case during its infectious period—"R") sampling from this distribution for cases with unknown infection date was included in the bootstrap and for all other analysis such a case was divided across possible dates proportionally to the distribution. For the few cases with unknown importation status, this value was imputed (included in the bootstrap for the calculation of R and divided amongst imported/indigenous proportionally for all other analysis) using the weekly likelihoods of a case being imported, calculated from the information available. For the weeks without any information the likelihood from the previous week was assumed, starting at week 1 with 100% imported.

Reproduction number

The effective reproduction number was calculated from the laboratory confirmed cases by an extended version of a method described by Wallinga and Teunis (2004) which uses the serial interval to assign a most likely source case for each case that was not imported and therefore estimates the average number of secondary cases caused by an individual (effective reproduction number). This included a correction for censoring as well as bootstrapping with re-sampling the unavailable data on importation status and date of illness onset. The serial interval distribution employed was constructed through artificial count data of 1,4,7,6,4,2,1,1 observations (representing weights) of a serial interval of length 0 to 7 days respectively. It was inspired by unpublished early estimates of the serial interval in the UK to follow a gamma distribution with mean of 3.88 days, variance of 2.77 days and an offset of 1 day (this estimate was slightly refined later to a mean of 2.51 days and a variance of 1.55 days without offset (Ghani et al., 2009)). To test for a difference between the R estimates of England compared to the other countries we examined the overlap between the confidence intervals, which is a rather conservative test (Schenker and Gentleman, 2001). To avoid setting up multiple data-sharing agreements, program code (written in R version 2.11.0) was distributed to each country to perform the analysis on its own data. Outputs from the program code were shared and analysed centrally.

Potential regulators for transmission

Chance

The probability of an outbreak of A(H1N1)v in a susceptible homogeneously mixed population becoming extinct (extinction probability) was approximated by a branching process (Karlin and Taylor, 1975). Given the daily number of importations for each country we assumed R to be similar to levels observed in England and negative binomially distributed. We calculated the daily extinction probability for each country for a set range for R and 3 scenarios of the variance to mean ratio representing transmission dynamics to be little, moderately and highly dependent on super spreading events (see Supplementary data).

Relative susceptibility of adults and the elderly compared to children

Age-susceptibility profiles were estimated for each country using the age-mixing information on both all contacts and close contacts obtained from Mossong et al. (2008). For countries that did not participate in that study, an averaged mixing pattern was assumed. The expected age distribution of cases was derived by a simple multiplication of the age distribution of the observed infected cases

Table 1

Overview of the countries' study period ends, the dates for closure of the first school due to summer holidays, the total number of confirmed cases, the respective percentage of imported cases and those with missing information on their travel background and the estimated effective reproduction number before onset of summer holidays.

	End of study period	First day of summer holidays	Confirmed cases	Imported	Unknown travel history	R before summer holidays
Belgium	13/07	01/07	126	61.3%	0%	0.19 (0.15–0.2)
Bulgaria	23/10	22/05	127	37.6%	0.6%	NA
England	23/06	22/07	4847	9.9%	0%	1.14 (1.11–1.17)
France	30/06	02/07	335	71.7%	1.9%	0.31 (0.29–0.39)
Germany	01/08	25/06	9193	79.6%	0%	0.52 (0.51–0.54)
Italy	30/06	05/06	146	86.3%	2.7%	0.08 (0.08–0.11)
Luxembourg	14/09	16/07	227	61.2%	15.4%	0.16 (0.11–0.16)
Netherlands	16/08	03/07	636	72.5%	4.3%	0.4 (0.38–0.42)
Portugal	20/08	09/07	2240	27.9%	0.2%	0.22 (0.21–0.24)
Romania	14/09	12/06	329	79.4%	0%	0.31 (0.31–0.32)
Slovakia	03/08	01/07	78	88.5%	0%	0.06 (0.06–0.06)
Spain	28/06	19/06	746	20.4%	0.3%	0.83 (0.82–0.83)

with the country specific mixing matrix. The expected and the observed number of secondary cases were divided into aged <20 y (children), aged ≥ 20 y but <60 y (adults) and aged ≥ 60 y (elderly). The relative susceptibility of adults vs. children and elderly vs. adults was estimated by the relative standardised incidence ratio in children, adults and elderly (for further details see Supplementary material). Bootstrap techniques were used to estimate confidence bounds. These included resampling of the observed age distribution from a Poisson distribution and the uniform sampling of one of the known mixing matrices for those countries where no such information exists. A random effects meta-analysis following the approach of [DerSimonian and Kacker \(2007\)](#) and using the log of the mean susceptibility estimates and its standard deviation was done to get a random effects pooled estimate of the relative standardised incidence ratio.

Age distribution of imported cases

The difference in age distribution (in 5-year age bands) of imported cases before the country specific start of the summer holidays of England compared to each other country was tested employing a two-sided Kolmogorov–Smirnov test.

Mixing patterns

Differences in expected age-distribution of secondary cases caused by an average infected person for England compared to Belgium, Germany, Italy, Luxembourg and the Netherlands were assessed using the data from a recently conducted contact survey ([Mossong et al., 2008](#)). We took 10,000 bootstrap samples for each countries' contact matrix (all contacts) and compared the respective dominant eigenvectors (which, scaled to 1, represents the targeted age-distribution of secondary cases) in the Euclidian norm. Empirical p-values were calculated.

School holidays

In most countries the start of the summer holidays depends on the type of school and region. To simplify matters we defined country-specific summer holidays as the period between the first day of school closing and the first day of school reopening (For Germany and the Netherlands this is a major simplification). Data on school closure for summer holiday was obtained from the respective sites ([Feiertagskalender](#); [Roditelli.bg](#)). The study period (P) was divided into term-time (P1) and, where data were available, the vacation period (P2).

Weather

Daily data on weather patterns (pressure, relative humidity, temperature and wind speed) were obtained from the Wolfram server using Mathematica 7. Unweighted countrywide daily averages were obtained from half hourly measures for all cities inhabited by more than 100,000 people. In Luxembourg this was extended to all cities. The Antoine equation ([Antoine, 1888](#)) was used for calculating absolute humidity.

Regression analysis

An additive mixed model analysis ([Wood, 2006](#)) was used to model the country-specific estimates of the effective reproductive number (on a log-scale) with time whilst accounting for the heterogeneity between and homogeneity within countries using a country-specific random intercept and an autoregressive correlation structure. The explanatory variables were: the cumulative number of importations, the extinction probability ($R=1.1$, variance to mean = 1), the absolute and relative humidity, the temperature, the air pressure, the wind speed, whether or not schools were closed for summer holidays and the number of days since the beginning of summer holidays (to represent the successive closure in different regions for some countries). In addition to a nonparametric model for

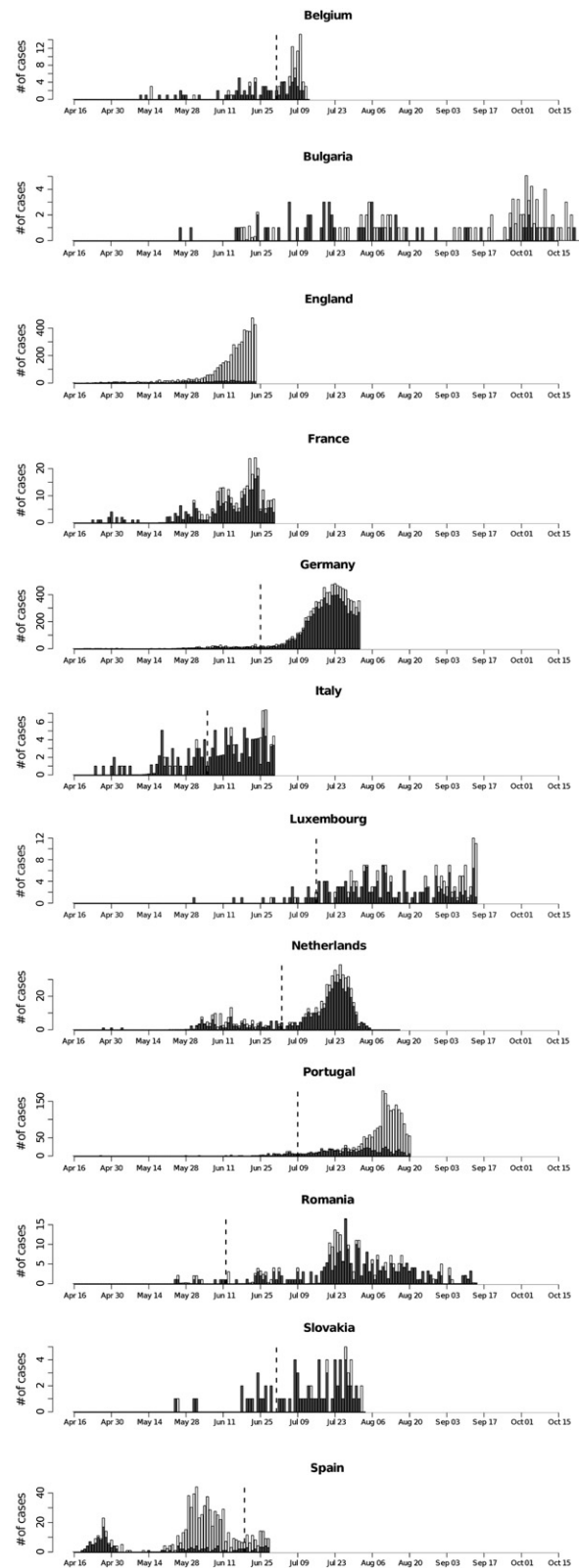


Fig. 2. Timeline of infection for the participating countries and their respective study periods. Cases coloured in dark grey are imported and the ones in light grey are indigenous. The vertical dotted line indicates the start date of summer holidays.

the country-specific evolution of the effective reproductive number over time, more specifically cubic regression splines, the model was augmented with explanatory variables thought to be predictive for

the observed differences in country-specific profiles. The Akaike Information Criterion (AIC) was used to select the best model amongst an extensive set of candidate models based on various combinations of the country-specific nonparametric time effect and the explanatory variables, balancing goodness of fit and model complexity (see Supplementary material for further detail).

Results

The country-specific end of the study period is provided in Table 1 along with the start date of school holidays and the total number of cases included in the analysis. Whilst in Bulgaria the first case occurred after the start of summer holidays in France and England the end of testing of all suspected cases was prior to the start of the summer holidays (Fig. 2). Case definitions differed only slightly by country (Table S1).

Whilst in most countries the majority of cases reported travel to a high-risk country within 7 days before symptom onset, in England over 90% of the cases were infected via in-country transmission. In the period before the country-specific onset of summer holidays we estimated the average number of secondary cases per case in all countries to be well below 1 (Table 1). Only in England R was significantly higher. The course of the reproduction number estimates over time for the 12 different countries during the summer of 2009 (Fig. 3) reveals that, with two exceptions, R was well below 1 (most remained below 0.5) the whole time until early August with some sporadic transmission clusters appearing afterwards (Figure S2). Spain had a reproduction number higher than 1 around mid-May – which corresponded to a few outbreaks associated with a military camp and several schools, but these did not result in ongoing community transmission. In England (and elsewhere in the UK (Ghani et al., 2009)) the reproduction number initially appeared to be around 1 but by mid-May was greater than 1, leading to increasing chains of transmission. Baguelin et al. (2010) show that the reproduction number remained above 1 until schools were closed at the end of July (the apparent decline in the reproduction number in the middle of June in our estimates shown in Fig. 3 is likely due to a decline in reporting efficiency as case-based reporting started to cease).

The recommendations for containment measures to limit the spread of the initial A(H1N1)v cases were broadly similar amongst the countries (i.e. containment efforts in England were not disparate from the others). Most countries offered antiviral treatment for all confirmed cases as well as antiviral prophylaxis for close contacts (Table S2). Only minor differences in recommendations for social distancing were reported. Using school closures to reduce the spread of A(H1N1)v was rarely used in all countries except England (about 70 closures until 23rd of June) and France (>4 in June).

The age distribution of imported cases before summer holidays was similar across Europe (Figure S3 and Table S3) with only the

Netherlands and Spain being significantly different than England. In Spain about 75% of the imported cases prior to summer school holidays were 20–30 years of age which results in a lower proportion of <20 year olds as well as >30 year olds than was observed in the UK. In all countries the majority of imported cases occurred in the 20–40 years old population with few imported cases in the other age groups. The expected age-distribution of secondary cases (as calculated from a contact survey in 2005/06) in England was not significantly different to those in Italy and the Netherlands (p :0.26 and 0.35). However, we found differences comparing England to Luxembourg (p <0.05), Belgium (p <0.05) and Germany (p <0.01) which are most apparent in an expected higher proportion of secondary cases of age 5–14y in England (Figure S4).

In all countries with enough cases to estimate whether there was a significant difference in susceptibility between adults (between 20–60 years) and children (<20 years), children were more susceptible (Fig. 4). The pooled estimate of relatively susceptibility of adults vs. children was 0.56 (0.46–0.69) assuming transmission to occur through two way conversational contacts (as reported in Mossong et al., 2008) and 0.69 (0.58, 0.84) through physical contacts only. As suggested elsewhere (Miller et al., 2010) we found the elderly to benefit from a better protection than other age groups. The pooled estimate of relative susceptibility of elderly vs. adults was 0.23 (0.16–0.32) assuming transmission through conversational contacts and 0.23 (0.16–0.33) through physical contacts only. Neither for adults nor for the elderly does England appear to be an outlier, with its susceptibility profile being not significantly different from pooled estimates.

We evaluated the likelihood of chance alone driving the observed difference in epidemiology, i.e. that the reproduction number actually was at similar or slightly lower levels as observed in England, but that outbreaks linked to importations terminated by chance in all other countries. Mechanisms that increase the probability of extinction are low numbers of secondary infections (i.e. if $R \leq 1$ an outbreak will have an extinction probability of 1) and a high contribution of super spreading events to the overall transmission. Whilst the average number of secondary infections in England and Wales until summer was estimated to be well above 1.1 (Baguelin et al., 2010; Ghani et al., 2009) in large countries other than England with a relatively high number of importations (Spain, France, Germany and the Netherlands), the probability that the chains of transmission would have terminated by chance given any true reproduction number ≥ 1.1 was calculated to be essentially zero by the middle of June for our low and medium scenario of variance to mean ratio (i.e. 5 or less). Even assuming the scenario of super spreaders playing a major role in transmission the joint probability of not observing a major epidemic in any large European country other than England by the middle of June (i.e. before school holidays in most countries) and presuming $R \geq 1.1$ in each country during that time would be smaller than 0.03 (joint probability on June 15th for France, Germany, Italy and Spain given the ratio of variance to

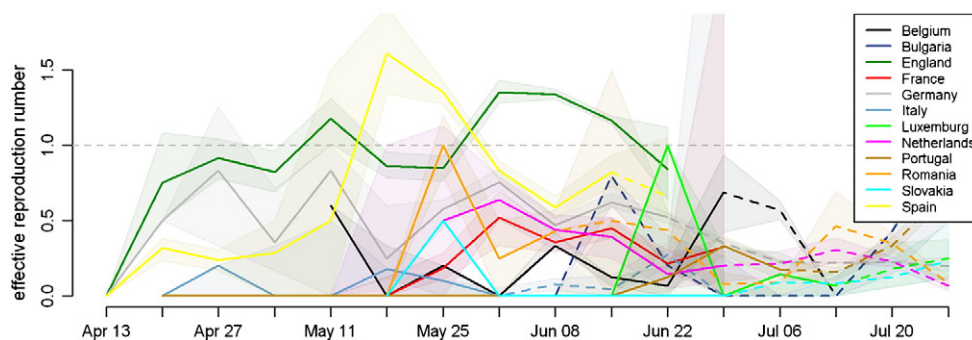


Fig. 3. The effective reproduction number (weekly aggregated) during the summer in the participating countries until the end of July when most in countries school holidays had started (see Figure S4 for the full time course); the dashed line indicates P2 (summer holidays) and the solid one P1 (no school holidays). The respectively coloured shaded area corresponds to the 95% confidence bounds.

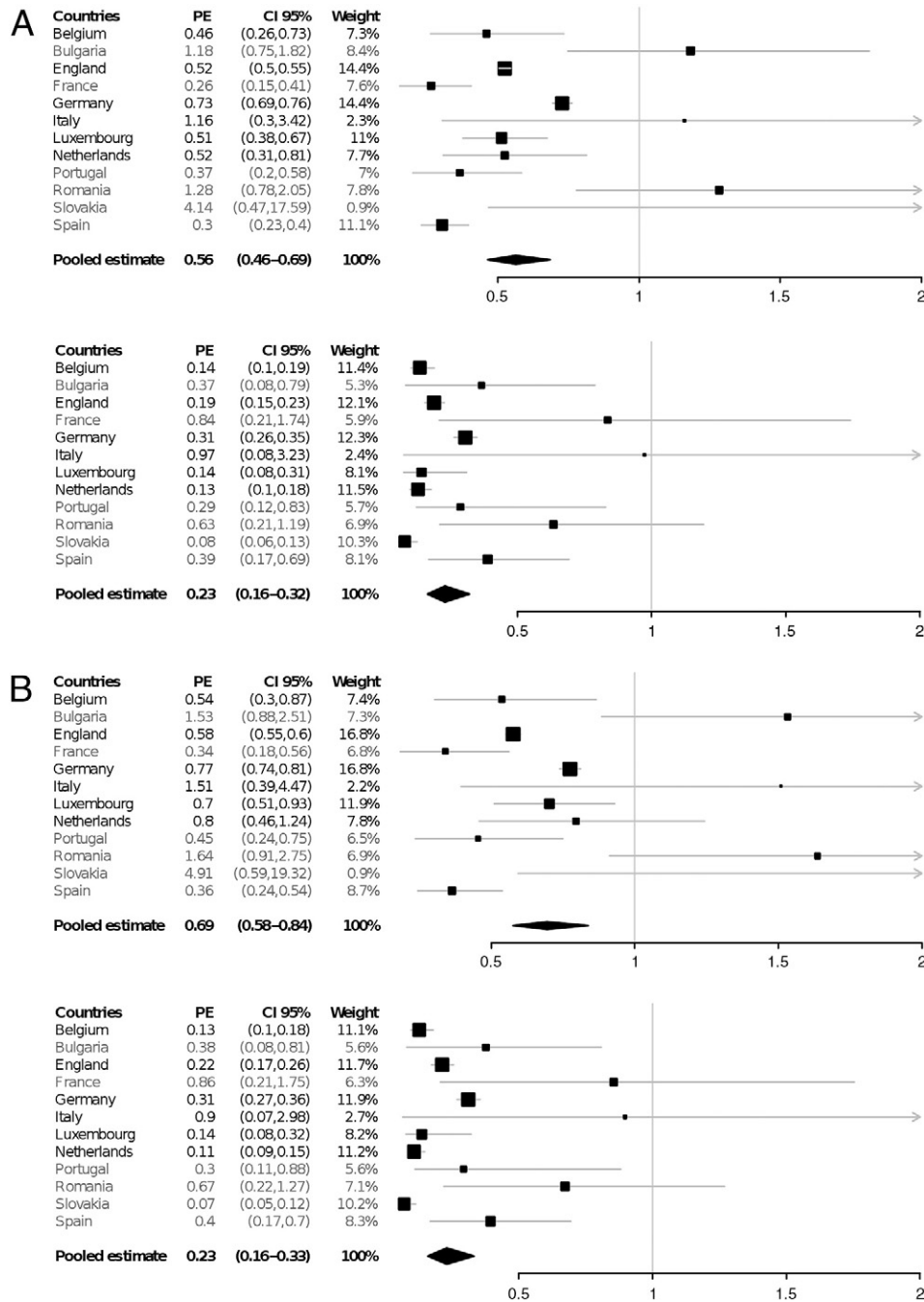


Fig. 4. The point estimates (PE) and their 95% confidence intervals for the estimated relative susceptibility of adults (≥ 20 and < 60 years) to children (< 20 years) and of elderly (≥ 60 years) to adults (top to bottom), using all contacts (A) and only physical contacts (B) as reported by a recent contact survey (Mossong et al., 2008). Countries named in grey did not take part in the study and therefore an average mixing pattern was assumed.

mean equals 25 and $R = 1.1$). Even in countries with few importations (mainly small countries and those with low rates of travel with North America), it is highly unlikely that they would have escaped a major epidemic by the end of July had the reproduction number actually been in excess of 1.1 (assuming low–medium variance to mean ratios (see Fig. 5)). By the end of June the joint probability of all countries in this analysis other than England not experiencing a major epidemic was smaller than 10^{-4} for $R \geq 1.1$ in all three transmission scenarios and it would have needed an R as low as 1.04 for the extinction probability to exceed 0.05.

We regressed the weekly aggregated effective reproduction number in the different countries using a large set of country-specific

explanatory variables (extinction probability, school holidays and several weather patterns). Only the extinction probability and the absolute humidity (Figure S5) were retained in the model based on the AIC criterion (Table S4). Since both the extinction probability and absolute humidity are time varying covariates, each of the two variables was replaced by two new variables separating the country-specific average and trend (for further information see Supplementary material). A residual analysis showed no multicollinearity amongst these variables and time. The final model explained 60.5% of the overall variability in the reproduction number (with 3% being explained by the variables in the model and the rest by spline effects) and showed a significant negative effect of the average extinction

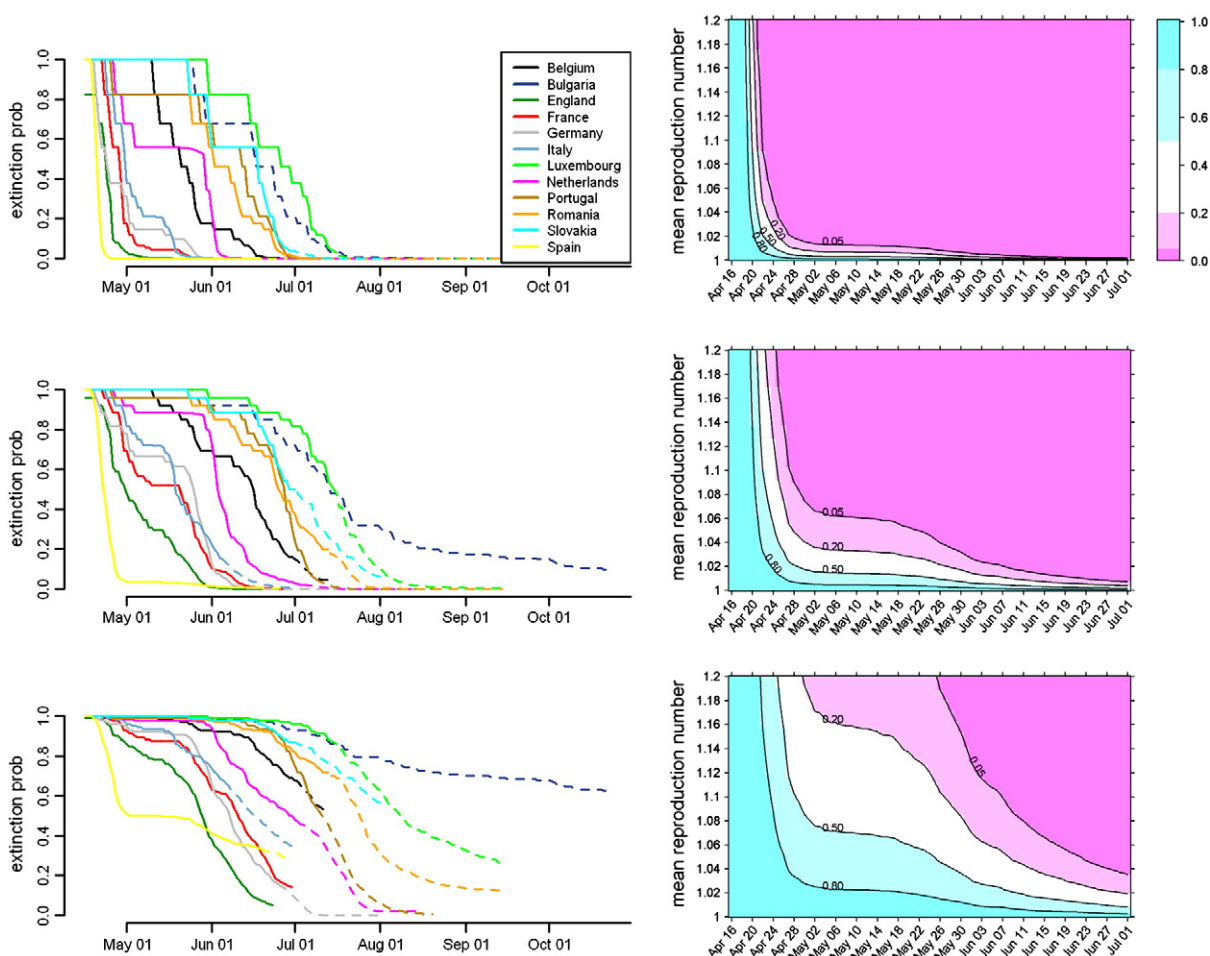


Fig. 5. Left column: time varying extinction probability for $R=1.1$ and variance to mean = 1,5,25 (top to bottom) given the imported cases of the different countries. The lines become dashed when school holidays started. Right column: joint extinction probability of all countries but England in early summer according to different values of the reproduction number with variance to mean being 1,5,25 (top to bottom).

probability ($p < 0.001$), the trend of the extinction probability ($p < 0.01$) and the trend in absolute humidity ($p < 0.05$) whereas the average absolute humidity was not retained in the final model based on the AIC criterion (Fig. 6). The nonparametric country-specific time effects were shown to be significant for Bulgaria, England, France, Italy, Luxembourg, Portugal, Romania and Spain expressing a non-linear evolution over time.

In the last weeks of the study period an increasing amount of suspected cases in England and France were no longer tested and presumed to be infected with A(H1N1)v. In our analysis we included only the confirmed cases but did some sensitivity analysis including the presumed cases. This showed no difference in the age-distribution and susceptibility and only minor differences in the weekly R estimates without affecting the general outcome (Figure S6).

Discussion

The emergence of the novel influenza A(H1N1)v in Mexico and the US was followed by only sporadic outbreaks limited in size and associated with imported cases across Europe in the late spring and summer of 2009 with the UK being the only exception. This was observed in the European ILI/ARI surveillance (Fig. 1). From mid-July until September many countries reported cases returning from various Mediterranean holiday regions. Spanish data suggests that these cases arose from local outbreaks confined to tourist areas rather than reflecting widespread transmission in the resident populations of holiday-destination countries. Our

estimates for the effective reproduction number based on laboratory-confirmed cases confirm that in the late spring and summer of 2009, transmission of novel influenza A(H1N1)v was not sustained across Europe, with the exception of England.

Although there are differences in the reporting of influenza-like-illness across Europe, our analysis focussed on laboratory-confirmed cases during the period of initial spread in each country. The laboratory and epidemiological definitions employed were broadly consistent across countries. Furthermore, we focus on the reproduction number which relies on the relative differences of reported cases over time rather than the absolute differences and is therefore relatively robust to varying levels of reporting between countries, although it is sensitive to short term alterations in reporting behaviour.

We found no evidence that the containment strategy (represented through antiviral treatment, school closures and social distancing) in England was less rigorous than in all of the other countries. Therefore the observed differences in transmission in England (and the rest of the UK) and other countries are unlikely to be solely the consequence of differences in containment, as they were broadly similar across the countries in this analysis, although there is no information available on the actual public compliance (Ferguson, 2007). Moreover, we show that contact patterns are similar in the UK to elsewhere in Europe with only small but significant differences between England and some of the countries. However, no such data exists for half of the studied countries so much uncertainty remains. It has become increasingly clear that children are particularly important for the spread of A

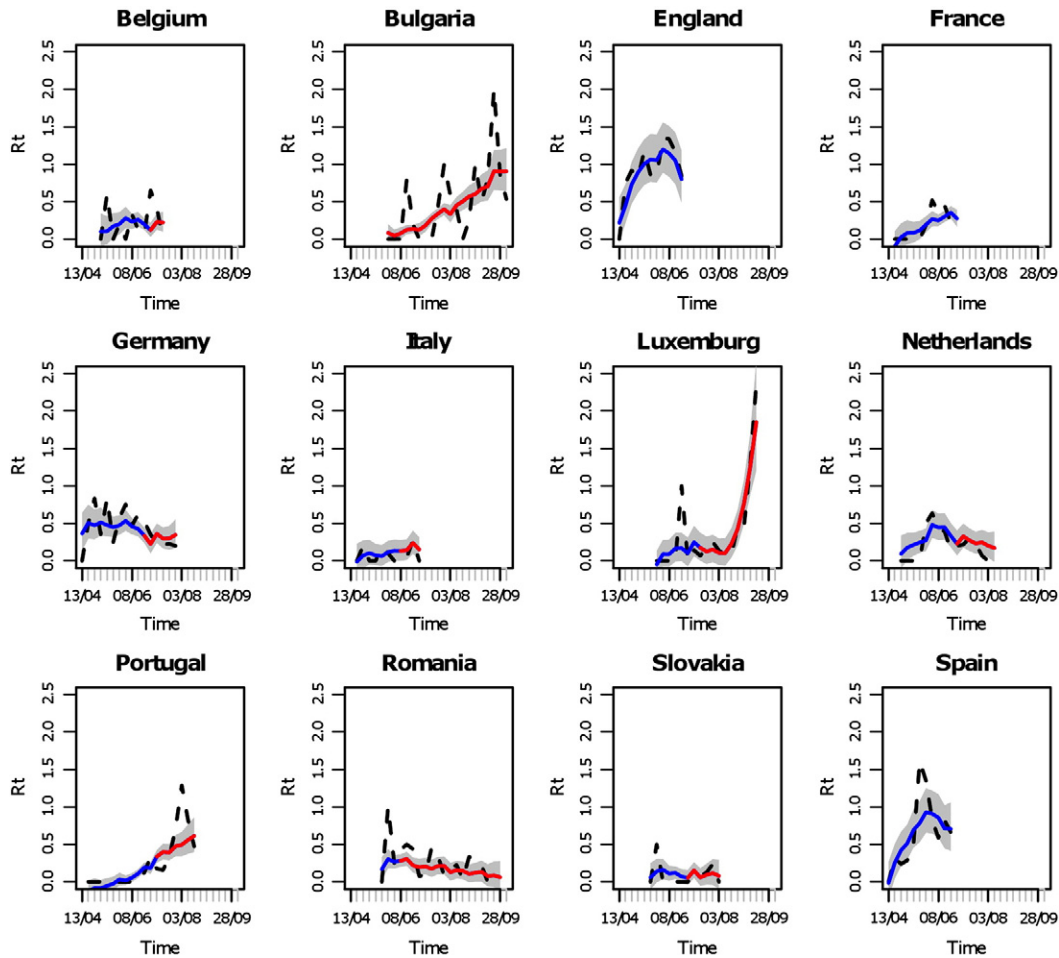


Fig. 6. The effective reproduction number (weekly aggregated) evolving in time in the participating countries (black dashed line) with predicted profiles based on additive mixed model (blue solid line for P1 and red solid line for P2) with 95% confidence intervals (grey shaded region).

(H1N1)v (see, for instance, Fraser et al., 2009). Our analysis suggests that there does not appear to have been a different susceptibility profile in England compared with other countries, nor was the age distribution of imported cases before the summer holidays different; however, these findings could have been altered by varying age-dependent reporting rates. Also the emergence of a different and more transmissible A(H1N1)v virus in England is unlikely to have occurred (Fereidouni et al., 2009).

Furthermore, it is improbable that differences in importation patterns on their own were sufficient to generate this anomaly. Since the extinction probability is converging to 1 for R approaching 1 extinction by chance can never be ruled out for all $R > 1$ but we show that for similar and even lower levels than observed in the UK the probability of the chains of transmission simply fading out by chance in all other countries was vanishingly small.

Even though school closures due to summer holidays were found to have substantially reduced the ongoing spread of A(H1N1)v in England (Baguelin et al., 2010) our analysis could not detect a significant role for summer holidays on the reproduction number. Possible factors which might have contributed to that finding include: 1) assessing the impact of school closure not being possible for some countries, as the holiday period was outside the study period, notably in England; 2) the impact of vacations on reducing the average number of secondary infections in the absence of sustained spread (as for all countries but England) might be outweighed by stochastic effects and therefore hardly detectable; 3) alterations in reporting

coinciding with school holidays might also have influenced the analysis. Neither the regression analysis nor a second method we employed (see Supplementary data; Table S5) could detect any consistent changes in R after the start of the summer holiday. It seems apparent that transmission limiting factors were already in place before summer holidays in all countries except the UK.

The only factors that appeared to be significantly related to the reproduction number from the regression analysis (although not retained for all scenarios in the sensitivity analysis – see Supplementary data) were the average and trend in the extinction probability if the reproduction number was 1.1 and the trend in absolute humidity, though the latter failed to fully explain it. The extinction probability is correlated with the cumulative number of importations (though the cumulative number of imported cases was not found to be significant when substituted into the model for the extinction probability), so a possible explanation for the negative association between the extinction probability and R could be a threshold corresponding to a number of importations needed to overcome the initial stochasticity. Alternative explanations could include that intervention strategies are more effective when there are only a few importations. The negative association between the trend in absolute humidity (AH) and R is in line with the recent findings from Shaman et al. (Shaman and Kohn, 2009; Shaman et al., 2010) who suggested a negative effect of absolute humidity on both transmissibility and the survival of the influenza virus and found an association of the daily variation in absolute humidity with the onset

of seasonal wintertime influenza outbreaks. Our finding that the baseline (average AH for each country) was not significantly associated suggests that the relation between R and AH may not represent a physical one but rather a change in human behaviour responding to changes in AH.

Taken together these results tentatively suggest that a possible explanation for the difference in epidemiology was that the UK had a relatively large number of early importations, transmission dynamics which were slightly favouring the spread in school-aged children and a relatively low level of absolute humidity. Perhaps widening this analysis to other countries and regions across the globe would help refine or refute these hypotheses. The program code (using the freely available language R) can be requested from the corresponding author and would enable other interested researchers to estimate these key parameters from the basic data set which was used in this paper. This could, therefore, help to build up a larger database on which questions about transmissibility of influenza can be tested. The code could also prove useful for analysing future influenza outbreaks.

This study highlights the fact that our current understanding of the transmission of influenza, in terms of distribution of susceptibility within the population and observed contact patterns assuming equal effectiveness of control measures does not fully account for the observed differences in the initial epidemiology of influenza A(H1N1)v in Europe. Further understanding of the precise mechanism behind such an association is crucial to help us predict the future spread of influenza more accurately and to design more efficient means to mitigate its impact.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at doi:10.1016/j.epidem.2011.03.005.

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