The geographic spread of influenza

ERIC BONABEAU¹, LAURENT TOUBIANA², ANTOINE FLAHAULT²

(1) Santa Fe Institute, 1399 Hyde Park Road, Santa Fe, NM 87501, USA
(2) INSERM - U444, B3E - ISARS, CHU Saint-Antoine, 27 rue Chaligny, 75012 Paris, France

SUMMARY

How infectious diseases spread in space within one cycle of an epidemic is an important question that has received considerable theoretical attention. There are, however, few empirical studies to support theoretical approaches, because data is scarce. Weekly reports obtained since 1984 from a network of general practitioners spanning the entire French territory allows the analysis of the spatiotemporal dynamics of influenza over a fine spatial scale. This analysis indicates that diffusion over long distances, possibly due to global transportation systems, is so quick that homogeneous global mixing occurs before the epidemic builds up within infected patches. A simple model in which the total number of cases is given by the empirical time series and cases are randomly assigned to patches according to the population weight of the patches exhibits the same spatiotemporal properties as real epidemic cycles: homogeneous mixing models constitute appropriate descriptions, except in the vicinity of the epidemic's peak, where geographic heterogeneities play a role.
1. INTRODUCTION

Models developed by epidemiologists are aimed at predicting epidemics or evaluating the efficiency of vaccination (Kermack & Mc Kendrick 1927; May & Anderson 1984; Anderson & May 1991; Anderson 1994; Hethcote 1978; Hethcote & Van Ark 1986; Mollison 1977; Grenfell et al. 1995; Post et al. 1983). A number of models incorporate real data, some among these include heterogeneities in the form of age structure or interaction networks (Anderson 1994; Hethcote 1978; Post et al. 1983; Hethcote & Van Ark 1986; Mollison 1977; Grenfell et al. 1995; Woolhouse et al. 1997; Bolker & Grenfell 1993, 1996; Ferguson et al. 1996), but few deal with the spatial component of epidemics (Baroyan et al. 1971; Cliff 1995; Cliff et al. 1986; Murray & Cliff 1975; Noble 1974; Cliff & Haggett 1988) despite the importance of understanding the geographic spread of infectious diseases. This can be understood as it is hard to find long and reliable epidemic time series, and virtually impossible to find good spatiotemporal data with fine-grained sampling scales. A remarkable dataset in that respect is the UK measles incidence case records, which span 40 years at more than 2000 locations, with up to several millions of cases reported per year. This dataset has been extensively studied and remarkable results have been found regarding the often subtle but important effects of space (Murray & Cliff 1975; Grenfell et al. 1995; Bolker & Grenfell 1996).

The existence of a network of general practitioners (GP) in France (Valleron et al. 1986) evenly distributed over the French territory since 1984 allowed us to obtain good-quality data (detailed reports exist for detected cases) on a weekly basis on a relatively small spatial scale (20 km). The number of GPs involved in the sentinel network has increased significantly since the network was launched, now representing 1% of all French GPs. Consequently, the size of the influenza dataset, which is the focus of the present study, reaches several thousand reports within an
epidemic cycle of about 15 weeks. Results presented in this paper are given for all epidemic cycles between 1987 and 1995. One question of particular interest is whether or not geographic space, including heterogeneities in population distribution, is relevant to the spread of the epidemic within a cycle. If space is not relevant, global mixing models give accurate descriptions of the epidemic process. If, on the other hand, space does play a role, spatial models incorporating local mixing and locally density-dependent dynamics, may be more appropriate. In terms of immunization, the two descriptions have different consequences (May & Anderson 1984; Anderson & May 1991; Bolker & Grenfell 1996) (uniform vs differential immunization). There has been some evidence in the past that space is indeed relevant to the spread of epidemics, and that epidemics spread with spatial waves from an initial epidemic center (Cliff 1995; Cliff et al. 1986; Murray & Cliff 1975; Noble 1974; Cliff & Haggett 1988). There is also some evidence that the local dynamics of an epidemic, characterized for example by its force of infection or basic reproduction number, depends on heterogeneities in population density (May & Anderson 1984; Anderson & May 1991), although the topic remains somewhat controversial and the dependence may be complex. Transportation systems have changed in the last 30 years, not only promoting exchanges among countries, but also within countries. Although global exchanges did exist 30 years ago (for example, retrospective modelling of the 1968 Hong Kong pandemic suggested that the virus had diffused rapidly, less than two years, through a worldwide network of interconnected cities (Rvachev & Longini 1985)), they may have been seriously amplified to the point where the timescale of global mixing is so short that it dominates over local dynamics. This also points to the crucial problem of the speed at which a vaccine should be developed in response to a new pandemic.

2. CORRELATION ANALYSIS
Fig. 1 shows the weekly time series of the total number of cases reported by the GP network over the entire territory between 1984 and 1995. The first four cycles that can be seen in Fig. 1 will be not be used in our study because of the imperfect coverage of the French territory by the network at that time. In order to study the influence of space on the spread of the epidemic within each period of the oscillatory incidence pattern, spatial correlations have been computed. Spatial data are binned in square patches of linear size $s$ km, hereafter called $s$-patches. Let $N_s(r,t)$ be the number of cases reported during week $t$ in the $s$-patch centered on location $r$. Let $n_s(r,t) = N_s(r,t)/P_s(r)$ denote the “normalized” version of $N_s(r,t)$, where $P_s(r)$ is the total population in the $s$-patch centered around $r$: $n_s(r,t)$ represents the per capita incidence data. Fig. 2 shows the equal-time density-density autocorrelation function $C_s(h,t)$ of $n_s(r,t)$ at the peaks of the last 8 epidemic cycles observed in Fig. 1. $C_s(h,t)$ is defined by

$$C_s(h,t) = \frac{\langle \langle [n_s(r,t) - \bar{n}_s][n_s(r+y,t) - \bar{n}_s] \rangle \rangle_{r,|y|=h}}{\sigma^2(n)} ,$$  

where $t$ is the time in weeks, $\langle \ldots \rangle_r$ denotes averaging over $r$ and $\langle \ldots \rangle_{|y|=h}$ averaging over $|y|=h$, $\bar{n}_s = \langle n_s(r,t) \rangle_r$ is the average spatial value of $n_s(r,t)$ and $\sigma^2(n) = \langle [n_s(r,t) - \bar{n}_s]^2 \rangle_r$ is the spatial variance of $n_s(r,t)$. The spatial distribution of the French population has been obtained from the French Institut Géographique National (last 1990 census survey). The correlations in $n_s(r,t)$ can be reasonably well characterized by $C_s(h,t) \propto h^\alpha$ with $\alpha = 0.04 \pm 0.03$, that is, a flat correlation function. This observation is confirmed when the same quantity, $C_s(h,t)$, is plotted for the whole dataset (Fig. 3). The best global fit of the type $C_s(h,t) \propto h^\alpha$ for the cloud of points represented in Fig. 3 is for $\alpha = -0.05 \pm 0.06$. This result suggests that the distribution of cases is randomly distributed over the territory, with the number of
cases in each patch being roughly proportional to the population of the patch. When the correlations of the raw incidence data $N_s(r,t)$, rather than those of its normalized value $n_s(r,t)$, are studied, long-range correlations are obtained (Bonabeau et al., 1998): such long-range correlations reflect the spatial structure of the underlying population distribution and not intrinsic spatial properties of the epidemic. It can therefore be misleading to use absolute incidence: *per capita* incidence data should always be preferred.

3. NULL HYPOTHESIS

A test of the suggestion made in the previous section –that the spread of the epidemic is statistically uniform in geographic space– consists of studying the empirical relationship between the epidemic’s spatial extent (number of infected patches) and its incidence (number of cases). The number of new reported cases per patch, $N_s(r,t)$, implicitly includes a threshold procedure: only in those regions where the actual number of cases exceeds some threshold can we expect reports to be issued. The spatial extent provided by the GP network may therefore not be the true extent of the epidemic but rather the number of regions in which the number of cases has exceeded the threshold. On the basis of this information, the following null hypothesis can be tested. Let $I_t$ be the total number of detected cases at time $t$ over the whole territory and $P$ the total population. The null hypothesis assumes that the $I_t$ detected cases are randomly distributed in space among all the regions of linear size $s$ according to their demographic weights –in other words, incidence is merely correlated with local population density.

In order to simulate this hypothesis, each of the $I_t$ cases is assigned to a zone: a zone $i$ (of linear size $s$ around point $r_i$) is chosen at random, and the case is assigned to zone $i$ with probability $P_s(r_i)/P$; if zone $i$ is rejected, another zone is
picked at random and tested, and this procedure is repeated until all cases are assigned to a zone. The relationship found between the size of the epidemic and its spatial extent observed in the data can be compared to the one obtained with the shuffled data. This method is similar to the surrogate data method used in time series analysis (Theiler et al. 1992): spatially distributing the cases among zones according to their demographic weights leads by construction to the same spatial correlations as those observed in the data.

Fig. 4 shows the number of infected patches as a function of the number of reported cases in the data and in 1000 simulations of the null hypothesis. One cannot easily discriminate between the null hypothesis and the data, except at the peak of the epidemic, indicating that the epidemic "spreads" more rapidly than it builds up within a given patch until it reaches its peak, where the real spatial extent of the epidemic saturates at a slightly lower value than the simulated one. In both the data and the simulation, three regimes are observed: (1) before and after the epidemic (number of reported cases<20), where there is a close-to-linear relationship between the spatial extent and the number of cases, (2) an intermediate phase (20<number of reported cases<200) where the number of infected patches increases sublinearly with the number of reported cases, and (3) the vicinity of the epidemic's peak (N>200), where the number of infected patches saturates. The small difference between the real and simulated spatial extent in regime (3) is likely to result from the following factors: in the simulation, the spatial extent saturates as the epidemic covers most of the territory, whereas in reality, it saturates because the epidemic reaches highly populated regions where contact rates may be higher, so that the number of cases increases in these regions more than in other regions.

4. BASIC REPRODUCTION NUMBER
On the basis of the previous sections’ observations, it is tempting to conclude that the data reflect a random distribution of cases according to demographic weight, and that the epidemic propagates mainly through a globally mixing process, possibly because of global transportation systems (Flahault et al. 1988, 1994). The dynamics of the global incidence (that is, the total number of cases over the whole territory) is a mean-field dynamics defined mainly at the global level under **homogeneous mixing.** Density dependence seems to play a role only in the vicinity of the epidemic’s peak. When a region becomes infected, the number of cases in that region increases, but the macroscopic spread of the epidemic is more rapid than its microscopic dynamics, so that a mean-field regime is reached before local dynamical heterogeneities can dominate. Only when the epidemic reaches its peak do such heterogeneities come into play, because of the build-up of the epidemic within densely populated infected patches.

If this theory is valid, the basic reproduction number, denoted by $R_0$, should not vary significantly between patches up to some large population density value, above which $R_0$ becomes greater. In order to test this prediction, $R_0$ can be approximated within a discrete time formalism (where 1 unit=1 week) by $R_0 \approx n^{T_n}$, where $T_n$ is the number of weeks it takes for the *per capita* incidence to be multiplied by $n$ (here, $n=2,3$) (Dietz 1993). This approximation results from the fact that the initial steps of the epidemic can be described by a geometric process with parameter $R_0$. Regions in which the *per capita* incidence does not double or triple within the whole epidemic cycle are not taken into account. More precisely, the following procedure is applied to estimate $R_0$:

1. Each cycle of the oscillatory incidence pattern is studied separately, starting 20 weeks before the peak of the cycle.
(2) The first time, $t_1$, when the \textit{per capita} incidence $n_1$ becomes greater than or equal to $5.10^{-6}$ (that is one case for $2.10^5$ inhabitants), is reported in a given s-patch (s=20 kms) is monitored. Both $t_1$ and $n_1$ are recorded. The doubling time $T_2$ is defined by $T_2 = t_2 - t_1$, where $t_2$ is the first time, if applicable, when the \textit{per capita} incidence exceeds $2n_1$. If the \textit{per capita} incidence does not double within the epidemic cycle, the data corresponding to the patch is discarded.

(3) The tripling time $T_3$ is computed in very much the same way as the doubling time $T_2$. $T_3$ is defined by $T_3 = t_3 - t_1$, where $t_3$ is the first time, if applicable, when the \textit{per capita} incidence exceeds $3n_1$. If the \textit{per capita} incidence does not triple within the epidemic cycle, the data corresponding to the patch is discarded.

We found no simple relationship between population density (PD, where PD is the average geographic density within a patch and does not exceed 2500 inh. km$^{-2}$) and $R_0$, as already suggested by numerous authors (e.g., de Jong \textit{et al.} 1995). However, larger values of $R_0$ are obtained for larger values of PD. For $0 < PD \leq 1300$ inh. km$^{-2}$, a cloud of $R_0$ values ranging from 1.09 to 1.732 can be observed. For $1300 < PD < 2500$ inh. km$^{-2}$, two clearly separated clouds of data points can be observed, which correspond to (1) regions where $R_0$ is comparable to the one found for $0 < PD \leq 1300$ inh. km$^{-2}$, and (2) regions where $R_0$ is larger ($R_0 = 2$ or 3). Some high-density patches yield larger $R_0$ estimates than others: because PD is the average PD within patches, two patches with the same PD may have quite different spatial organizations and contact rates; how the population is spatially distributed within patches can influence $R_0$. Despite the biases inherent in the computation of $R_0$, the observed difference in $R_0$ between some highly populated regions and other regions seems to confirm that the difference between the null hypothesis (Section 3) and the data results from a heterogeneity in contact rates that becomes apparent only when the epidemic reaches densely populated regions.
5. DISCUSSION

In order to be completely sure that the apparent global mixing does not result from the annual flare-up of an already locally circulating infection (influenza can be maintained in small populations), one would need to know the antigenic types of all recorded cases, all the more as influenza is subject to antigenic drift. However, about 15% of all reported cases were tested during the 1994-1995 epidemic cycle and indicate a strong proportion of two type A strains (53% H3N2 and 41% H1N1). This suggests that most of our analysis should be correct: models assuming global homogeneous (and instantaneous, within a week) geographic mixing are appropriate to describe the initial spread of the epidemic; geographic heterogeneities and density dependence play a role only in the few weeks around the epidemic’s peak.

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REFERENCES


Figure captions

**Fig. 1**: Time series of the number of cases of influenza reported by the French network of GPs (Sentinelles) between 1984 and 1995. Twelve peaks can be observed. Only the last eight cycles are used in the study. Definition of a case: sudden appearance of fever $>39\degree C$, myalgia and respiratory problems. 166 infecteds have been tested for an influenza virus during the 1994-1995 epidemic: 94% had type A viruses (53% H3N2 and 41% H1N1), and 6% had a type B virus.

**Fig. 2**: Log-log plot of the spatial equal-time density-density autocorrelation function $C_s(h,t)$ of $n_s(r,t)$, the number of reported cases normalized by the size of the population, at scale $s=20$ km. The 8 represented curves correspond to the peaks of the last 8 epidemic cycles of Fig. 1. $C_s(h,t)$ can be reasonably well characterized by $C_s(h,t) \propto h^\alpha$ with $\alpha = 0.04 \pm 0.03$.

**Fig. 3**: Log-log plot of $C_s(h,t)$ for the whole 1987-1995 dataset. The best global fit of the type $C_s(h,t) \propto h^\alpha$ for the cloud of points is for $\alpha = -0.05 \pm 0.06$.

**Fig. 4**: Number of infected patches as a function of the number of reported cases in the data and in 1000 simulations of the null hypothesis. The null hypothesis consists of assigning cases to patches in proportion to their demographic weights. In the empirical dataset, error bars along the x-axis correspond to putting $I_i$ into bins and averaging over all data points within each bin, and error bars along the y-axis correspond to averaging over all spatial extents obtained for each bin. The empirical data set aggregates all data between 1987 and 1995. Error bars in the simulated data correspond to averaging over 1000 simulations. The spatial scale for both the data and the simulations is $s=20$ km.