Influenza epidemics occur once a year during the winter in temperate areas. Little is known about the similarities between epidemics at different locations. We have analyzed pneumonia and influenza deaths from 1972 to 1997 in the United States, France, and Australia to examine the correlation over space and time between the three countries. We found a high correlation in both areas between France and the United States (correlation in impact, Spearman’s $\rho = 0.76$, $p < 0.001$, and test for synchrony in timing of epidemics, $p < 0.001$). We did not find a similar correlation between the United States and Australia or between France and Australia, when considering a systematic half-year lead or delay of influenza epidemics in Australia as compared with those in the United States or France. These results support a high correlation at the hemispheric level and suggest that the global interhemispheric circulation of epidemics follows an irregular pathway with recurrent changes in the leading hemisphere.

Influenza epidemics occur each year during the winter in temperate areas of the Northern and the Southern Hemispheres and result in substantial disease, death, and expense. The disease is responsible for 50 million illnesses and up to 47,200 deaths in the United States each year (1–3), with similar figures in Europe (4–6). In the last century, three global epidemics, also called pandemics, occurred in 1918-19, 1957-58, and 1968-69, and recent reports estimate that the 1918-19 influenza pandemic alone may have caused as many as 50 million deaths (7). Changing strains of the virus are responsible for these epidemics, but little is known about what triggers the epidemic in a particular location (2,8), and how epidemics observed at different locations may be linked (9–12). Travel has been thought to be a possible cause after mathematical models based on population movements successfully explained the 1968-69 pandemic (10) and represented the paths of the epidemic within a country (9,11,12). While the cause of the geographic spread of influenza is still debated, the reasons for its seasonality are even more unclear. Although markedly seasonal, the exact timing of the winter epidemics varies from year to year. Furthermore, the interannual impact of influenza epidemics varies substantially (1,3,4).

Documenting patterns in the space and time dynamics of influenza epidemics is the first step in understanding the underlying mechanisms driving epidemic fluctuations (13). Correlations over time and space have been estimated for several animal and insect populations (14–16) and diseases such as measles (17–19) but not for influenza, despite the increasing availability of time series with the recent development of surveillance networks (3,20–28). We provide data and a statistical analysis for the correlations over time and space for influenza-related deaths in the United States, France, and Australia during a 26-year period which spans 1972–1997. Our goal was to determine whether influenza epidemics are correlated in impact and synchronized in time 1) at the hemispheric level and 2) at the interhemispheric level with a systematic half-year lead of one hemisphere to the other.

Datasets and Models

Datasets

In each country, the weekly number of deaths from pneumonia and influenza from 1972 to 1997 were computed from death certificates collected by national agencies for vital statistics (United States, National Center for Health Statistics; Australia, Australian Bureau for Statistics; France, Institut National de la Santé et de la Recherche Médicale, Service Commun 8). We used codes
and France for the 26 years considered, and 2) influenza epidemics in Australia were systematically 6 months behind.


data analysis
From the pneumonia and influenza death series, we investigated two aspects of influenza epidemics: the correlation in impact as measured by seasonal excess death rates and the synchrony in timing of the epidemic peaks.


definition of epidemic and excess deaths
Influenza epidemic activity is typically observed during November–March in the United States and France and June–September in Australia (8). We conducted analyses by using the influenza year, which runs from the first week of August to the last week of July of the next year in the United States and France and contains one annual epidemic. We considered the regular calendar year as the influenza year in Australia. From the national weekly pneumonia and influenza death time series, we defined the epidemic periods by a similar procedure to that described by Serfling and used by the Centers for Disease Control and Prevention (CDC) (29,30). In summary, we excluded 25% of the weeks in which the observed death rates were the largest to exclude epidemic periods. We then fit a seasonal regression model to the truncated series to estimate the expected baseline number of deaths in the absence of epidemic activity. A nonepidemic threshold was defined by the upper limit of the 95% confidence interval derived from the seasonal regression model. Only influenza activities that remained above the threshold for ≥2 consecutive weeks were included in the analysis. For each influenza year, we measured the excess deaths by subtracting the expected baseline deaths, calculated from the seasonal regression model, from the observed deaths.

estimating correlation in excess deaths from influenza epidemics
We calculated pair-wise Spearman correlation coefficients of the excess deaths estimated for each of the 26 influenza years in the study period for the three countries. For France and the United States, epidemics were paired for contemporaneous influenza years. To test for correlation between the United States and Australia or between France and Australia, we investigated two pairing scenarios: 1) influenza epidemics in Australia were systematically 6 months in advance of those of the United States and France for the 26 years considered, and 2) influenza epidemics in Australia were systematically 6 months behind.

estimating synchrony in timing of peaks of influenza epidemics
For each influenza year and each country, we defined the week of the year when the peak of the epidemic occurred as the week where the maximal number of pneumonia and influenza deaths was observed. Then, we determined the distribution of the time lags between the weeks of the peak in France and in the United States in contemporaneous influenza years, with negative values of the time lag indicating that the epidemic in France preceded that in the United States. The same distribution was calculated for Australia and the United States and for Australia and France, with the two scenarios detailed in the previous section for pairing. We expected the time lags of the peaks in the United States and France to be distributed around zero if the assumption of synchronism of the peaks held true, with a small variance indicating high synchrony.

To test whether the reported distribution of the time lags was indicative of synchrony, we simulated the distribution of these lags when there was no particular synchronization mechanism between these two countries except for the seasonality of the disease. We randomly permuted the week when the pneumonia and influenza death time series peaked in the United States for the 26 influenza years and computed the distribution of the lags with the original series from France. A p value for the existence of synchrony in the peaks was derived from this randomization procedure.

With regards to Australia, because of the change of hemisphere, we expected the week of the peak to lag by 6 months on average with that of the United States or France, regardless of the pairing scenario. Here again, the small variance of distribution of the time lags would indicate synchronism. For both pairing scenarios, we performed a randomization procedure similar to that described for comparing France and the United States to derive a p value for synchrony in the peaks.

results
Figure 1 depicts the raw time series of weekly number of deaths from pneumonia and influenza in the United States, France, and Australia, normalized by population size. The series show a typical seasonal pattern, with large interannual variability in the amplitude of epidemics in all three countries. The pneumonia and influenza death series for Australia appears less smooth than for the United States or France, probably because of noise effects caused by the smaller population size of Australia, representing 7% of the population size of the United States and 32% of that of France.
Excess Deaths

For the 26 influenza years (1972–1997), we estimated a median of 26 per million population pneumonia and influenza excess deaths in the United States (range 0-63), 39 per million pneumonia and influenza excess deaths in France (range 0-183), and 13 per million pneumonia and influenza excess deaths in Australia (range 0-75). The rates of excess deaths were different in the three countries (Kruskal-Wallis test, p = 0.02). The Table gives the detailed annual estimates of the number of excess deaths for each influenza year. Two of 26 influenza years in the United States did not result in substantial excess pneumonia and influenza deaths, 4 in France, and 3 in Australia. The duration of the epidemic periods was similar in France and in the United States, with an average duration of 11.8 weeks in the United States (standard deviation (SD) = 0.8) and 11.4 weeks in France (SD = 0.8, p = 0.80, Wilcoxon rank test). The epidemic periods in Australia were shorter than those in the United States and in France, with an average duration of 9.6 weeks (SD = 1.0; Kruskal-Wallis test, p < 0.001).

Correlation in Excess Deaths

The correlation coefficient for excess deaths in the United States and France in contemporaneous influenza years was high (Spearman’s ρ = 0.76, N = 26, p < 0.001; Figure 2A). On the contrary, excess deaths in Australia were not correlated with excess deaths in France or the United States in the scenario in which Australia was systematically 6 months behind (Spearman’s ρ = 0.15 for Australia and the United States, p = 0.47 and Spearman’s ρ = 0.17 for Australia and France, p = 0.37).

Synchrony in Timing of Peaks

In France and in the United States, in the 26 influenza years, the median time lag between the weeks when the peak occurred was half a week (N = 26, range –8 through 6) reflecting a high level of synchrony (Figure 3A). The peak occurred earlier in the United States in 11 of the 26 epidemic seasons, earlier in France in 13 epidemic seasons, and on the same week for both countries in 2 epidemic seasons. Influenza epidemics did not peak earlier in France more often than in the United States, or vice versa (chi square, p = 0.66). Of the 100,000 randomizations we performed by permuting the week of the peak, 2 gave a variance for the time lags lower than that reported for the original data (Figure 4A; p < 0.001). Therefore, these results show synchronism in the times of peaks between France and the United States.

In the scenario in which the influenza season in Australia was systematically 6 months in advance of that in the Northern Hemisphere, the median time lag between the peaks in Australia and in the United States was 27 weeks (range 14-39) and 26 weeks between those in Australia and in France (range 15-41; Figure 3B and C). In the scenario in which the influenza season in Australia was systematically 6 months behind that in the Northern Hemisphere, these lags were 25.5 weeks (range 13-36) and 24.5 weeks (range 13-34), respectively. The simulated distributions obtained from the 100,000 permutations of the
week were not different from the observed distributions (in the scenario in which the influenza season in Australia was 6 months behind, \( p = 0.70 \) and \( p = 0.79 \) for the United States and France, respectively [Figure 4B and C] and in the scenario in which it was 6 months in advance, \( p = 0.13 \) and \( p = 0.12 \). For these two pairing scenarios, no synchrony in the peaks was evident.

**Discussion**

The results of this study favor a high level of correlation in amplitude and synchrony in the timing of influenza epidemics in France and the United States. No correlation or synchrony was found between Australia and the United States, or between Australia and France in the two scenarios in which Australia systematically led or lagged behind the global interhemispheric circulation of epidemics by 6 months.

The level of correlation in amplitude evidenced here depends on the statistical method used for estimating seasonal excess deaths. We have used a similar procedure to that described by Serfling and used by the CDC for estimating excess deaths (3,29). In our study, periods of increased influenza activity were excluded from the baseline model by discarding upper marginal values that were above a somewhat arbitrary cutoff (25th percentile of the distribution), and we found a high correlation between excess deaths in the United States and France (Spearman’s correlation coefficient \( \rho = 0.76 \)). The correlation remained stable with a lower cutoff set at 10%: in this analysis the correlation coefficient was also 0.76. Moreover, our excess death estimates are well in line with those published for the United States (3,31,32) and for France by using a different statistical approach (4). For the United States and France, the correlation coefficients between our estimates of pneumonia and influenza excess deaths and the most recently published estimates were 0.87 and 0.94, respectively, with similar orders of magnitude (3,4). No comparable estimates were available for Australia. Pneumonia and influenza death series have been used traditionally since the work of William Farr in the late 1840s to quantify the effect of influenza epidemics in terms of death (33) because severe complications are triggered by influenza infection and result in death, in particular bacterial pneumonia (34). The use of pneumonia death series might

---

**Table. Number of pneumonia and influenza excess deaths and duration in weeks (wk, in parentheses) of influenza epidemics for each influenza year in the United States, France, and Australia, 1972–1997**

| Influenza season (Northern Hemisphere) | U.S. excess deaths (wk) | France excess deaths (wk) | Influenza season (Southern Hemisphere) | Australian excess deaths (wk) |
|---------------------------------------|------------------------|--------------------------|---------------------------------------|-------------------------------|
| 1971-72                               | 8,100 (9)              | 4,200 (13)               | 1972                                  | 200 (11)                      |
| 1972-73                               | 11,000 (13)            | 9,500 (13)               | 1973                                  | 250 (10)                      |
| 1973-74                               | 4,100 (15)             | 0 (0)                    | 1974                                  | 150 (6)                       |
| 1974-75                               | 9,000 (13)             | 7,000 (16)               | 1975                                  | 900 (14)                      |
| 1975-76                               | 13,600 (13)            | 4,800 (12)               | 1976                                  | 0 (0)                         |
| 1976-77                               | 600 (3)                | 1,400 (9)                | 1977                                  | 1,000 (16)                    |
| 1977-78                               | 10,000 (13)            | 2,500 (8)                | 1978                                  | 200 (8)                       |
| 1978-79                               | 0 (0)                  | 300 (4)                  | 1979                                  | 100 (7)                       |
| 1979-80                               | 4,200 (9)              | 0 (0)                    | 1980                                  | 250 (13)                      |
| 1980-81                               | 8,600 (10)             | 3,100 (11)               | 1981                                  | 200 (9)                       |
| 1981-82                               | 0 (0)                  | 0 (0)                    | 1982                                  | 0 (0)                         |
| 1982-83                               | 1,400 (5)              | 1,800 (10)               | 1983                                  | 700 (15)                      |
| 1983-84                               | 700 (4)                | 0 (0)                    | 1984                                  | 250 (12)                      |
| 1984-85                               | 7,000 (11)             | 2,200 (15)               | 1985                                  | 150 (8)                       |
| 1985-86                               | 6,000 (13)             | 4,700 (18)               | 1986                                  | 650 (15)                      |
| 1986-87                               | 2,000 (7)              | 900 (9)                  | 1987                                  | 0 (0)                         |
| 1987-88                               | 8,700 (18)             | 700 (8)                  | 1988                                  | 100 (7)                       |
| 1988-89                               | 7,000 (16)             | 1,000 (9)                | 1989                                  | 200 (9)                       |
| 1989-90                               | 10,400 (14)            | 4,300 (11)               | 1990                                  | 750 (17)                      |
| 1990-91                               | 3,300 (12)             | 1,000 (10)               | 1991                                  | 100 (6)                       |
| 1991-92                               | 6,800 (10)             | 2,900 (16)               | 1992                                  | 50 (3)                        |
| 1992-93                               | 6,300 (16)             | 2,100 (16)               | 1993                                  | 300 (14)                      |
| 1993-94                               | 9,800 (11)             | 2,600 (11)               | 1994                                  | 50 (3)                        |
| 1994-95                               | 5,300 (15)             | 900 (10)                 | 1995                                  | 300 (10)                      |
| 1995-96                               | 6,300 (16)             | 2,500 (17)               | 1996                                  | 100 (5)                       |
| 1996-97                               | 11,400 (18)            | 4,500 (13)               | 1997                                  | 250 (10)                      |

---

*Excess deaths reported from August of a given year to July of the next year during an influenza epidemic (e.g., for row labeled 1971-72, excess deaths occurring from August 1971 to July 1972).*

*Population, 272.7 million.*

*Population, 58.6 million.*

*Excess deaths reported from January to December of a given year during an influenza epidemic (e.g., for row labeled 1972, excess deaths occurring from January 1972 to December 1972).*

*Population, 18.9 million.*
introduce additional background noise in estimating excess deaths caused by influenza, especially because of the high level of activity in the summer and the upward trend observed since the early 1980s (6). We performed a sensitivity analysis by restricting our calculations of excess deaths to deaths coded as influenza only and retrieved a similar correlation between the United States and France (Spearman’s $\rho = 0.75$). However, we do not capture the total impact of influenza by analyzing only pneumonia and influenza death, which accounts for only part of the overall deaths from influenza (4,34). Therefore, we probably cannot rely strictly on our absolute estimates of excess deaths to study the overall impact of influenza epidemics on death. However, pneumonia and influenza deaths series provide a robust and unbiased indicator of the severity of influenza epidemics for between-country comparisons. In addition, with an indicator as simple and crude as the raw pneumonia and influenza deaths observed during the week of the peak, the correlation remains of the same order (Spearman’s $\rho = 0.73$).

Demography may contribute to the lack of correlation and synchrony between Australia and the United States or between Australia and France. While the age structures of the populations in the three countries are similar, the population sizes are different. Discrepancies in the levels of vaccination might also play a role. However, the number of doses of influenza vaccine distributed was similar in France and the United States from 1980 until the early 1990s but doubled in recent years in the United States (35). The level of vaccination in Australia was about half of that of France and the United States from 1980 until 1990 and became similar to that of France in recent years.

Figure 2. Correlation in the impact of influenza epidemics for 26 influenza years (1972–1997), measured by the annual number of pneumonia and influenza excess deaths. A, excess deaths per million in France (y axis) and the United States (x axis) in contemporaneous winters: Spearman correlation coefficient = 0.76 ($p < 0.001$). B, excess deaths per million in Australia (y axis) and the United States (x axis), considering the scenario in which the influenza season in Australia is systematically 6 months before that of the United States: Spearman correlation coefficient = 0.14 ($p = 0.50$). C, excess deaths per million in Australia (y axis) and France (x axis), considering the scenario where the influenza season in Australia is systematically 6 months before that of France: Spearman correlation coefficient = 0.37 ($p = 0.06$). We obtained similar results as in B and C, when we considered a reverse scenario in which the influenza season in Australia was systematically lagging 6 months behind that in the United States or France.

Figure 3. Synchrony in the timing of the peaks of influenza epidemics for 26 influenza years (1972–1997). Correlation between the week of year of the epidemic peak A, in the United States (x axis) and in France (y axis). B, in the United States (x axis) and in Australia (y axis). C, in France (x axis) and in Australia (y axis). Panels B) and C) illustrate the scenario in which the influenza season in Australia is systematically 6 months before that of the United States or France. Similar results are obtained for the reverse scenario.
Therefore, no obvious link existed between trends in vaccination and our results.

An important limitation in the analysis of correlation and synchrony between countries in different hemispheres lies in the arbitrary choice for pairing epidemics. We investigated two extreme scenarios in which influenza epidemics in Australia were systematically 6 months ahead of those in France or the United States or systematically 6 months behind. We found no correlation or synchrony in either one. We cannot rule out a more complex interhemispheric pathway with recurrent changes in the leading hemisphere. We searched for an optimal theoretical pairing, allowing each epidemic in Australia in our simulations to pair with either the preceding or following epidemic in the United States (or France) to maximize the correlation in excess death. For optimal pairing, the correlation coefficients obtained were in the same order of magnitude as those observed between France and the United States (Spearman’s $\rho = 0.66$ for the United States and Australia and Spearman’s $\rho = 0.71$ for Australia and France).

Few reports document the circulation of influenza virus on a worldwide scale. Hope-Simpson studies of death, disease, and virologic datasets suggest that the circulation of influenza strains (and the epidemics they cause) may follow a given pathway during several years (e.g., Southern to Northern Hemisphere) and subsequently shift to the other pathway (e.g., Northern to Southern Hemisphere) (36). This finding agrees with the absence of significant time and space correlations found in this work between countries in different hemispheres when epidemics were paired 6 months ahead or behind. If this absence of correlation between the two hemispheres, observed in death records limited to an interpandemic period and a limited set of countries, held true in the case of a pandemic, information on previous routes of transmission derived from historical epidemics (10,37) could prove of little use for planning the route of future epidemics or pandemics on a worldwide scale.

Our study nevertheless strongly suggests that influenza epidemics are correlated in amplitude and synchronized in timing in the Northern Hemisphere, and collection and analysis of additional data is underway in other countries of Europe and North America. Prevaccination measles epidemics in different locales of the United States and the United Kingdom were also highly correlated in time and space, a situation that evolved to the observed absence of correlation in the last 2 decades after the level of vaccination increased from 50% to 90% (17,19). This lack of correlation is reportedly promoting persistence of the disease (19). Space and time correlations of influenza epidemics may follow the same pattern as vaccine coverage increases. How the very high rate of antigenic evolution of influenza virus, a feature not found in measles, could impact on this change requires further study, all the more as antigenic variations explain partly the impact of the disease (3,19,38–40). The current plan to control influenza advocated by the World Health Organization promotes vaccine use and, in case of emergence of a pandemic virus, extensive use of antiviral drugs and vaccine, assuming that the vaccine could be produced in a timely fashion (41). The impact of an expected loss of correlations in influenza epidemics resulting from increased vaccine use should be further investigated, especially by mathematical modeling.

In conclusion, two factors have been reported to drive the space and time correlations of epidemics: population movements and environmental issues, such as climate or weather conditions (14–16). Population movements are assumed to play a key role, though not quantified, in the global spread of influenza epidemics (8,10), but the role of
environmental factors and virus circulation between the Southern and Northern Hemispheres (42–44) remains to be clarified. Large-scale molecular epidemiologic studies of influenza viruses, sampled from locations in different hemispheres, could assist in investigating the circulation pathways of the disease (44). Such large-scale studies seem feasible in light of the recent plan for a global sentinel laboratory that could centralize genotype and archive samples collected worldwide (45).

Acknowledgments
We thank T. Dunn, S. Erbacher, and F. Péquimot for providing the datasets.

The French Ministry of Education and Research and the Fondation pour la Recherche Médicale provided support for Cécile Viboud.

Dr. Viboud is a mathematical biologist with Fogarty International Center, National Institutes of Health. Her research interests focus on the modeling of influenza epidemics over time and space, with a particular emphasis on the transmission mechanisms.

References
1. Monto AS. Individual and community impact of influenza. Pharmacoeconomics 1999;16:1–6.  
2. Cox NJ, Subbarao K. Influenza. Lancet 1999;354:1277–82.  
3. Simonsen L, Clarke MJ, Williamson GD, Stroup DF, Arden NH, Schoenberger LB. The impact of influenza epidemics on mortality: introducing a severity index. Am J Public Health 1997;87:1944–50.  
4. Carrat F, Valleron AJ. Influenza mortality among the elderly in France, 1980–90: how many deaths may have been avoided through vaccination? J Epidemiol Community Health 1995;49:419–25.  
5. Fleming DM, Zambon M, Bartelds AI, de Jong JC. The duration and magnitude of influenza epidemics: a study of surveillance data from sentinel general practices in England, Wales and the Netherlands. Eur J Epidemiol 1999;15:467–73.  
6. Tillett HE, Smith JW, Gooch CD. Excess deaths attributable to influenza in England and Wales: age at death and certified cause. Int J Epidemiol 1983;12:344–52.  
7. Johnson NPAS, Mueller J. Updating the accounts: global mortality of the 1918–20 “Spanish” influenza epidemic. Bull Hist Med 2002;76:105–15.  
8. Cox NJ, Subbarao K. Global epidemiology of influenza: past and present. Annu Rev Med 2000;51:407–21.  
9. Baroyan OV, Rvachev LA, Basilevsky UV, Ezmakov VV, Frank KD, Rvachev MA, et al. Computer modeling of influenza epidemics for the whole country (USSR). Advances in Applied Probability 1971;3:224–6.  
10. Longini IM Jr, Fine PE, Thacker SB. Predicting the global spread of new infectious agents. Am J Epidemiol 1986;123:383–91.  
11. Flahault A, Deguen S, Valleron AJ. A mathematical model for the European spread of influenza. Eur J Epidemiol 1994;10:471–4.  
12. Flahault A, Letrait S, Blin P, Hazout S, Menares J, Valleron AJ. Modeling the 1985 influenza epidemic in France. Stat Med 1988;7:1147–55.  
13. Hayden DT, Stenseth NC, Boyce MS, Greenwood PE. Phase coupling and synchrony in the spatiotemporal dynamics of muskrat and mink populations across Canada. Proc Natl Acad Sci U S A 2001;98:13149–54.
14. Kendall BE, Bjornstad ON, Bascombe J, Keitt TH, Fagan WF. Dispersal, environmental correlation, and spatial synchrony in population dynamics. Am Nat 2000;155:628–36.  
15. Bjørnstad ON, Ims RA, Lambin X. Spatial population dynamics: analyzing patterns and processes of population synchrony. Trends Ecol Evol 1999;14:427–32.  
16. Earn DJ, Rohani P, Grenfell BT. Persistence, chaos and synchrony in ecology and epidemiology. Proc R Soc Lond B Biol Sci 1999;265:7–10.  
17. Cliff AD, Haggett P, Stroup DF, Cheney E. The changing geographical coherence of measles morbidty in the United States, 1962–88. Stat Med 1992;11:1409–24.  
18. Bolker BM, Grenfell BT. Impact of vaccination on the spatial correlation and persistence of measles dynamics. Proc Natl Acad Sci U S A 1996;93:12648–53.  
19. Grenfell BT, Bjørnstad ON, Kappey J. Traveling waves and spatial hierarchies in measles epidemics. Nature 2001;414:176–23.  
20. Flahault A, Dias-Ferrao V, Chabert P, Esteses K, Valleron AJ, Lavanchy D. FluNet as a tool for global monitoring of influenza on the Web. JAMA 1998;280:1330–2.  
21. Snacken R, Manuguerra JC, Taylor P. European influenza surveillance scheme on the Internet. Methods Inf Med 1998;37:266–70.  
22. Fourquet F, Drucker J. Communicable diseases surveillance: the Sentinel Network. Lancet 1997;349:794–5.  
23. Quenel P, Dab W. Influenza A and B epidemic criteria based on time-series analysis of health services surveillance data. Eur J Epidemiol 1998;14:725–25.  
24. Fleming DM, Zambon M, Bartelds AI. Population estimates of persons presenting to general practitioners with influenza-like illness, 1987–96: a study of the demography of influenza-like illness in sentinel practice networks in England and Wales, and in The Netherlands. Epidemiol Infect 2000;124:245–53.  
25. Goddard NL, Joseph CA, Zambon M, Nunn M, Fleming D, Watson JM. Influenza surveillance in England and Wales: October 1999 to May 2000. Commun Dis Public Health 2000;3:261–6.  
26. Hashimoto S, Murakami Y, Taniguchi K, Nagai M. Detection of epidemics in their early stage through infectious disease surveillance. Int J Epidemiol 2000;29:905–10.  
27. Snacken R. Weekly monitoring of influenza impact in Belgium (1993–1995). Pharmacoeconomics 1996;9:74–50,73–50.  
28. Fleming DM, Cohen JM. Experience of European collaboration in influenza surveillance in the winter of 1993–1994. J Public Health Med 1996;18:133–42.  
29. Serfling R. Methods for current statistical analysis of excess pneumonia influenza deaths. Public Health Rep 1963;78:494–506.  
30. Simonsen L, Clarke MJ, Stroup DF, Williamson GD, Arden NH, Cox NJ. A method for timely assessment of influenza-associated mortality in the United States. Epidemiology 1997;8:390–5.  
31. Choi K, Thacker SB. An evaluation of influenza mortality surveillance, 1962–1979. II. Percentage of pneumonia and influenza deaths as an indicator of influenza activity. Am J Epidemiol 1981;113:227–35.  
32. Lui KJ, Kendall AP. Impact of influenza epidemics on mortality in the United States from October 1972 to May 1985. Am J Public Health 1987;77:712–6.  
33. Farr W. Vital statistics: a memorial volume of selections from the reports and writings of William Farr. London: Office of the Sanitary Institute; 1885.  
34. Simonsen L. The global impact of influenza on morbidity and mortality. Vaccine 1999;17(Suppl 1):S3–5.  
35. Ambrosch F, Fedson D. Influenza vaccination in 29 countries: an update to 1997. Pharmacoeconomics 1999;16:51:47–54.  
36. Hope-Simpson RE. The transmission of epidemic influenza. New York: Plenum Press; 1992.  
37. Freeman R, Ellis J, Glass G. Assessing the impact of airline travel on the geographic spread of influenza. Eur J Epidemiol 2003;18:1065–72.
38. Plotkin JB, Dushoff J, Levin SA. Hemagglutinin sequence clusters and the antigenic evolution of influenza A virus. Proc Natl Acad Sci U S A 2002;99:6263–8.
39. Ferguson NM, Galvani AP, Bush RM. Ecological and immunological determinants of influenza evolution. Nature 2003;422:428–33.
40. Bush RM, Bender CA, Subbarao K, Cox NJ, Fitch WM. Predicting the evolution of human influenza A. Science 1999;286:1921–5.
41. Stohr K. The global agenda on influenza surveillance and control. Vaccine 2003;21:1744–8.
42. Colwell RR, Patz JA. Climate, infectious disease and health: an interdisciplinary perspective. Washington: American Academy of Microbiology; 1998.
43. Ebi KL, Exuzides KA, Lau E, Kelsh M, Barnston A. Association of normal weather periods and El Nino events with hospitalization for viral pneumonia in females: California, 1983–1998. Am J Public Health 2001;91:1200–8.
44. Earn D, Dushoff J, Levin S. Ecology and evolution of the flu. Trends Ecol Evol 2002;17:334–40.
45. Layne SP, Beugelsdijk TJ, Patel CK, Taubenberger JK, Cox NJ, Gust ID, et al. A global lab against influenza. Science 2001;293:1729.

Address for correspondence: Cécile Viboud, Fogarty International Center, National Institutes of Health, 16 Center Drive, Bethesda, MD 20892, USA; fax: 301 496 8496; email: viboudc@mail.nih.gov