Original Contribution

Influenza Epidemics in Iceland Over 9 Decades: Changes in Timing and Synchrony With the United States and Europe

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Influenza epidemics exhibit a strongly seasonal pattern, with winter peaks that occur with similar timing across temperate areas of the Northern Hemisphere. This synchrony could be influenced by population movements, environmental factors, host immunity, and viral characteristics. The historical isolation of Iceland and subsequent increase in international contacts make it an ideal setting to study epidemic timing. The authors evaluated changes in the timing and regional synchrony of influenza epidemics using mortality and morbidity data from Iceland, North America, and Europe during the period from 1915 to 2007. Cross-correlations and wavelet analyses highlighted 2 major changes in influenza epidemic patterns in Iceland: first was a shift from nonseasonal epidemics prior to the 1930s to a regular winter-seasonal pattern, and second was a change in the early 1990s when a 1-month lag between Iceland and the United States and Europe was no longer detectable with monthly data. There was a moderate association between increased synchrony and the number of foreign visitors to Iceland, providing a plausible explanation for the second shift in epidemic timing. This suggests that transportation might have a minor effect on epidemic timing, but efforts to restrict air travel during influenza epidemics would likely have a limited impact, even for island populations.

airline; Iceland; influenza; synchrony; transportation; wavelets

The incidence of disease caused by influenza virus follows a distinct seasonal pattern during interpandemic periods, with epidemics typically occurring during winter months in temperate areas of the Northern Hemisphere. The timing of influenza activity varies between years and geographic locations, and these variations have been linked to a number of factors including environmental conditions, social behaviors, and host immunity (1), as reviewed by Lipsitch and Viboud (2) and Tamerius et al. (3).

Both local and international transportation could affect the speed of epidemic spread and synchrony between distant locations. Although modeling work and empirical data have suggested that increased air travel should favor more rapid epidemic spread and synchronize epidemics globally (4–9), the presence of many international land, sea, and air connections in most countries can make it difficult to evaluate the role of air travel in promoting epidemic spread.

Iceland—an historically isolated island nation with a low population density, no land connections to surrounding countries, and robust disease surveillance records—provides an ideal setting for examining long-term changes in epidemic timing and assessing the role of international population movements and other contributing factors. All contact with foreigners relies on ship and airline traffic, with the latter dominating in recent years. The introduction of commercial, trans-Atlantic flights in the mid-1900s led to an explosion of international travel to and from Iceland with the annual number of foreign visitors increasing from just 5,000 in 1950 to nearly 500,000 in 2009 (10).

In this study, we examine changes in the timing and periodicity of annual influenza epidemics in Iceland since the mid-1900s in relation to epidemics in Europe and North America and evaluate the role of potential contributing factors to these changes such as international travel and environmental conditions.

MATERIALS AND METHODS

Data sources

Epidemiologic data. We compiled monthly and weekly influenza mortality and morbidity data from a variety of sources and countries that have disease surveillance records spanning 30 years or more, including Iceland, Denmark, France, and the United States.

Monthly influenza morbidity statistics from Iceland were obtained from the annual health reports (Heilbrigðisskýrslur) for the period from 1915 to 1975 (11) and from the Directorate of Health and the Icelandic national archives for subsequent years. These were derived from monthly disease-count reports from all general practitioners around Iceland covering the entire population.

Danish influenza morbidity data were drawn from 2 sources. For 1915–1993, cases of influenza-like illness were reported each week by all general practitioners around Denmark covering the entire population and compiled into monthly national statistics (the original weekly figures were not available). From 1994 through 2008, weekly data were obtained from a nationwide influenza-like illness sentinel surveillance system from select general practitioners around the country (12). These weekly data were collapsed by month, and the rates were standardized for the number of weeks in the month. Missing values for summer months in the latter data set were filled in using the minimum values from surrounding months.

Monthly influenza mortality data from the United States (underlying causes of death) were obtained from the annual *Vital Statistics* reports, obtained from the National Center for Health Statistics, 1915–2006. French influenza mortality data were obtained for 1968–1999 from the Institut National de la Santé et de la Recherche Médicale, Service Commun 8 (13).

The number of cases per month for each time series was adjusted for the number of days in the month (or number of weeks per month for the Danish sentinel surveillance data), and long-term trends were removed by dividing the monthly values by a smoothing spline fit through the average value for each 15-year period starting in 1915.

International travel and climate data. Statistics on the annual number of visitors traveling to Iceland and the nationalities for 1947–2007 were obtained from the Icelandic Tourist Board (14), Statistics Iceland (10, 15), and the Keflavík airport (Anna Dagný Halldórsdóttir, Isavia, personal communication, 2010). Travel data included the annual numbers of travelers to Iceland of American, British, German, and Nordic nationalities. Travel data for 2001 and 2002 were not available and were set to missing. Travel statistics were available by calendar year, rather than by July–June respiratory season, so we calculated the value for the season as the average between the values in the 2 consecutive years that comprised the season.

Monthly climate data were obtained from the Icelandic Meteorologic Office (16) and included temperature, precipitation, and relative humidity. Absolute humidity was calculated from temperature and relative humidity (17). For each July–June season, we determined the month of minimum absolute humidity or temperature.

As a control, we also considered factors that increase with time but should be unrelated to influenza timing, including exponential trend and number of registered cars in Iceland.

Epidemic timing. We measured changes in the timing of the annual influenza epidemics with 3 approaches. First, we determined which month in each 12-month period from July to the following June had the maximum influenza activity and calculated the number of months separating the epidemic peaks. Given that a well-defined peak is required to accurately estimate the month of peak timing, we excluded seasons with no significant influenza activity. Seasons with no influenza activity were defined as seasons in which the national influenza incidence did not exceed the upper limit of the 95% confidence interval of a seasonal threshold, derived from a Serfling (18) linear regression.

Second, we analyzed Pearson's correlation coefficients between each time series (detrended and square-root transformed) and the leads and lags of each of the other time series to determine at which time lag we observed the strongest correlation. Rolling correlations were calculated by using a centered 120-month window.

Third, we used continuous wavelet transformations (Morlet) (19) to calculate the phase of the annual epidemics in each country (R package developed by Johansson et al. (20)). The ends of the data were padded with excess zeros to reduce edge effects, and phase differences were transformed with the following: $mod(phase\ difference + 540, 360) - 180$, as described by Grenfell et al. (19). We used the average phase from wavelets with periods of 0.8–1.2 years. Phase differences were calculated as (phase in comparison country – phase in Iceland), with a positive value indicating that Iceland lagged behind the reference country. Phase difference data for the pandemic period from 1956–1957 to 1958–1959 were excluded from the analyses because these years showed irregular, nonseasonal peaks that were not appropriately captured by the 12-month wavelets. The mean phase difference for each month was calculated from the phase difference of Iceland versus Denmark, United States, and France, and the average of these mean values was determined for the period from December through March of each season.

Statistical analyses

The wavelet analyses were performed in R language (R Foundation for Statistical Computing, Vienna, Austria), and all other statistical analyses were performed in SAS, version 9.2, software (SAS Institute, Inc., Cary, North Carolina).

RESULTS

Change in the timing of the annual influenza epidemics

Prior to the early 1930s, the influenza epidemics in Iceland lacked a consistent seasonal pattern and included several peaks in the summer months (11) (Figure 1A) (Web Figure 1A posted on the *Journal*'s Web site (http://aje.oxfordjournals.org/)). During the 1930s, wavelet analyses
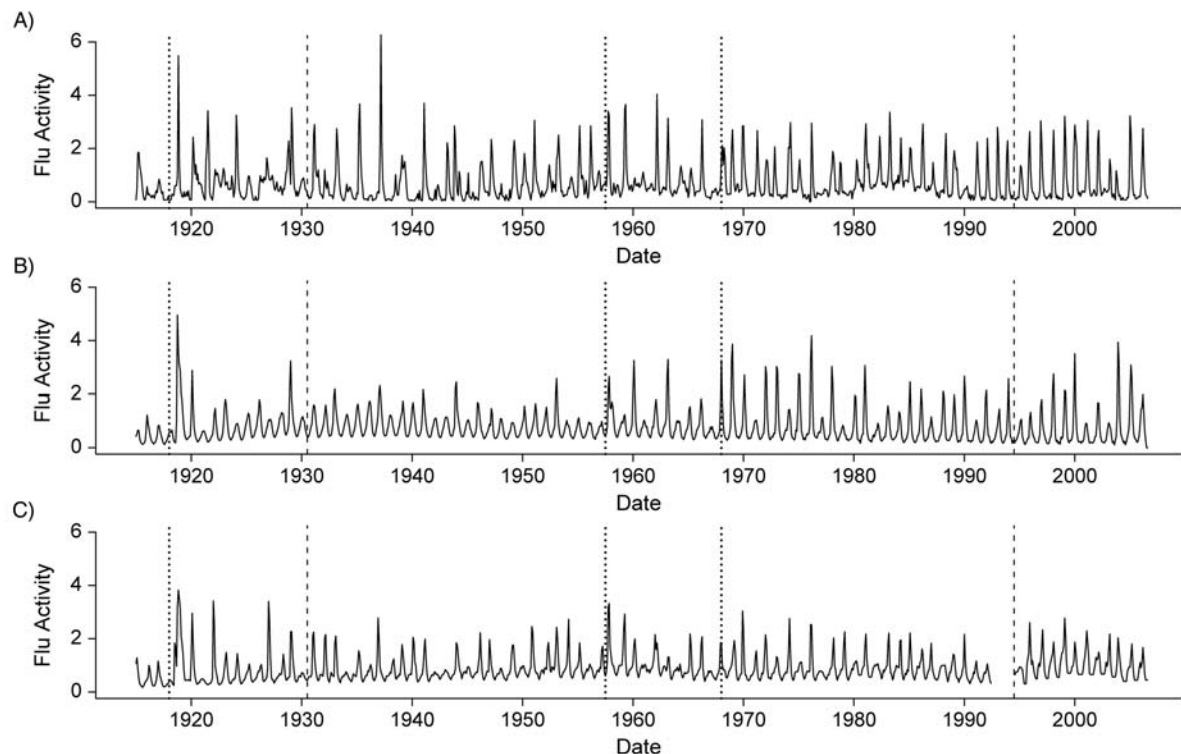
Figure 1. Monthly influenza activity, detrended and square root transformed, in Iceland (A), the United States (B), and Denmark (C), from 1915 to 2009. The dashed lines at midyear 1930 and 1994 indicate the transition periods, and the dotted lines at midyear 1918, 1957, and 1968 indicate the pandemic periods.

demonstrate both an annual and a 2-year cycle in the data, and after 1940, the annual cycle dominated (Web Figure 1, B and C). Because we were interested in seasonal epidemics, we focused on the period from 1933 to 2007. During these years, influenza activity in Iceland peaked between October and May in most seasons (Web Figure 2A). Interestingly, in the period from 1990 to 2007, there were no late-spring peaks in Iceland, and there was a significantly higher probability of having the peak occur between December and March compared with any of the preceding time periods ($P = 0.01$, Fisher's exact test). In contrast, influenza activity peaked in the United States between January and March in most years through the entire period (Web Figure 2C), and in Denmark, the peaks typically occurred between December and April (Web Figure 2B). Similar to Iceland, there were no late-spring epidemic peaks in Denmark after the early 1980s.

Difference in peak timing between countries

Looking simply at the number of months between the epidemic peaks in Iceland and the other countries, we found considerable year-to-year variability, with Iceland lagging behind the other countries by several months in some years and with no lag in other years (Figure 2A). Cross-correlation analyses demonstrate that the strongest correlations between Iceland and Denmark, between Iceland and the United States, and between Iceland and France occurred with a 1-month lag for the period 1933–

1993 (Table 1). In contrast, the correlation between Denmark and the United States was strongest with no lag, suggesting that the peaks in both countries occurred within 1 month.

Starting in the early 1990s, there were fewer years in which Iceland lagged substantially behind the other countries (Figure 2A). This shift is apparent when examining a rolling 10-year correlation between Iceland and the United States (Figure 2B). For most of the period, the correlation was strongest with the 1-month-lagged US time series, but starting in the 1990s, the correlation was greater between the unlagged US time series and the Icelandic time series (Figure 2B). A similar pattern was observed for the rolling correlations between Iceland and Denmark and between Iceland and France (not shown).

We next used wavelet analysis to measure how the lag between Iceland and the other countries changed over time. Similar to the results with the rolling correlations, the wavelets demonstrated that Iceland lagged behind the United States, Denmark, and France in most years until the 1990s, at which time the lag disappeared (phase difference of 0) (Figure 2C). There was also a period for several years in the 1970s in which there was a low phase difference among all 4 countries, followed by a period in the 1980s in which Iceland again lagged behind these other countries. The phase difference between the United States and Denmark and between the United States and France was stable over the whole period and centered around zero, indicating that there was not a consistent lag between these
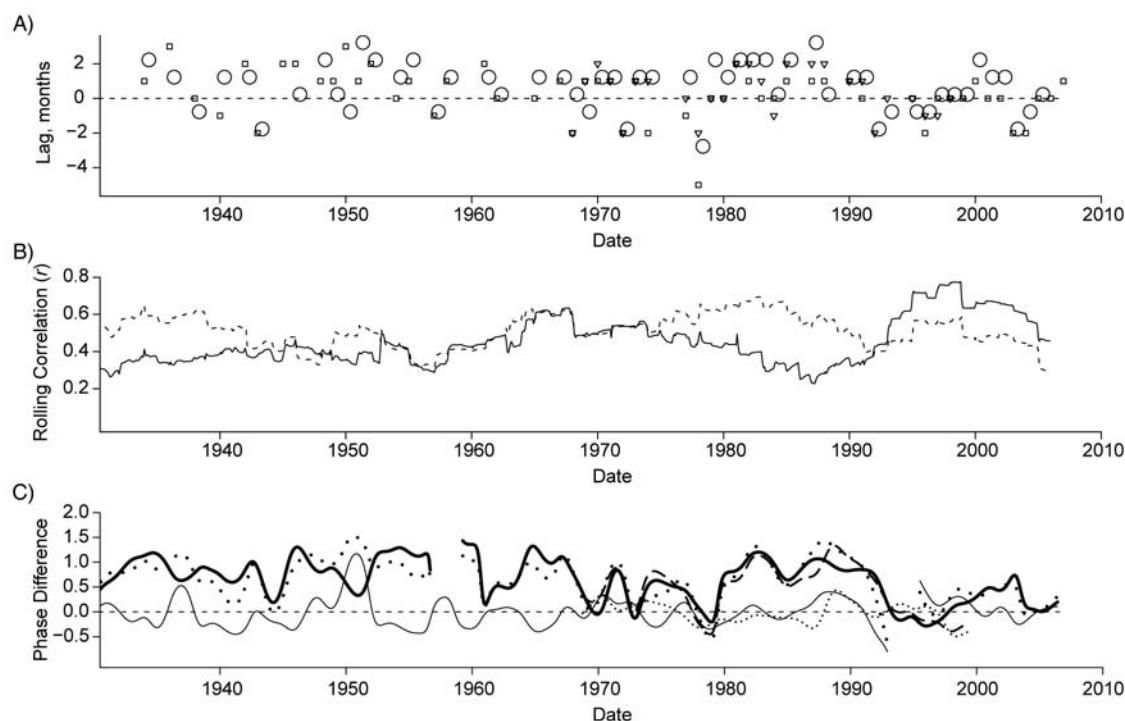
Figure 2. Changes in synchrony of influenza epidemics between Iceland and other countries over time from 1933 to 2007. The 3 panels depict the following. A, months between influenza peaks in Iceland and the United States (circles), Denmark (squares), and France (triangles). The years in which influenza incidence did not cross the seasonal threshold were excluded from this panel. Positive values indicate that Iceland lagged behind the comparison country. B, rolling 120-month correlation coefficient (*r*) between the United States and Iceland with a 1-month lag in the US series (dashed curve) or no lag (solid curve), showing changes in the strength of the correlation between these series over time. C, phase difference (radians) for Iceland versus Denmark (thick dotted curve), Iceland versus the United States (thick solid curve), Iceland versus France (dashed curve), the United States versus Denmark (thin solid curve), and the United States versus France (thin dotted curve).

time series in most years (Figure 2C). In fact, there was no detectable lag in the time series between the United States and Denmark as far back as 1915 (Web Figure 3).

Regional variation in the timing of influenza epidemics within Iceland

It was previously reported that epidemics in Iceland tend to originate in the capital, Reykjavík, and then spread outwards, and that the speed of spread has increased over time (11, 21). We considered the possibility that the apparent change in the timing of influenza epidemics could be biased by changes in the speed of spread within Iceland and by increasing population density in Reykjavik. To evaluate the potential influence of these changes, we used wavelets to calculate the timing of the influenza epidemics in the southwest region of the country (including Reykjavík) compared with the rest of the regions in Iceland combined. We found that, indeed, the annual epidemics did occur first in the areas surrounding Reykjavík, but this region still lagged behind the United States, Denmark, and France (Web Figure 4A). The influenza epidemics became more synchronous throughout the country over time, and the lag between the southwest and the rest of the country had mostly disappeared by the mid-1970s (Web Figure 4B). As a result, the shift in timing observed in the early

1990s is unlikely to be attributed to changes in population movement and density within Iceland.

Factors associated with increased synchrony between Iceland and other countries

Finally, we considered factors that could be responsible for changes in epidemic timing over the course of this period. We hypothesized that the shift in the average timing of influenza epidemics in Iceland could be related to the large increases in international contacts during the second half of the 1900s. In univariate analyses, increases in the number of travelers from the United States, Britain, Germany, and the Nordic countries were associated with smaller influenza phase differences between Iceland and the other countries. The strongest correlation was with the number of travelers from Germany, and the weakest association was with travelers from the Nordic countries (Table 2). We also found that, as a group, the total number of travelers from non-Nordic countries was associated with smaller phase differences between Iceland and the other countries.

Aside from travel, we evaluated other factors that might be associated with increased synchrony. There was no association between phase difference and the timing of the minimum of absolute humidity or temperature, nor was there a significant time trend in these environmental

Table 1. Cross-correlations of the Iceland, Denmark, and US Influenza Time Series, 1933–1993[a]

Lag/Lead, months	Iceland[b] vs. Denmark	Iceland[b] vs. the United States	United States[b] vs. Denmark
−4	0.08	−0.01	−0.18
−3	0.28	0.18	−0.02
−2	0.45	0.38	0.20
−1	0.54	0.49	0.45
0	0.46	0.40	0.61
1	0.18	0.18	0.52
2	−0.08	−0.06	0.26
3	−0.18	−0.22	−0.03
4	−0.22	−0.29	−0.25

[a] Negative numbers indicate lags of the comparison time series, and positive numbers indicate leads. For Iceland, the strongest correlation came when the comparison time series was lagged by 1 month (the Iceland peak occurred 1 month later), whereas the correlation between the United States and Denmark was strongest with no lags.

[b] Indicates the reference time series for each comparison.

Table 2. Univariate Correlations Between Relevant Factors and Average Phase Difference Between Iceland and the United States and Europe From 1947 to 2005[a]

	Pearson's r
Total foreign visitors	−0.54*
US visitors	−0.49*
British visitors	−0.52*
Nordic visitors	−0.49*
German visitors	−0.59*
Non-Nordic visitors	−0.56*
Icelanders travelling abroad	−0.48*
Exponential trend	−0.49*
Population size of Iceland	−0.50*
No. of cars in Iceland	−0.42*
Month of minimum humidity	−0.04 (NS)
Month of minimum temperature	−0.04 (NS)
Phase difference between southwest Iceland and the rest of the country[b]	0.47*

Abbreviation: NS, not significant.

* $P < 0.001$.

[a] Traveler variables were square root transformed. 1956–1958 (pandemic period) and 2001–2002 (missing travel data) were excluded from the calculations.

[b] Phase difference was available through 1974–1975 and then set to 0 (denoting no lag).

factors. The phase difference between southwestern Iceland and the rest of Iceland was positively associated with the phase difference between Iceland and the other countries—accounting for the short-term increase in synchrony during the 1970s. As a comparison, we also found a negative association between phase difference and exponential trend, Icelandic population size, and number of registered cars in Iceland. Out of all of the univariate factors, the number of German visitors was most strongly correlated with phase difference (Table 2).

In multivariate regressions, there was a moderate but significant association ($R^2 = 0.3$) between the number of non-Nordic travelers and phase difference between Iceland and the other countries when controlling for population size, exponential trend, or lag between southwest Iceland and the rest of the country.

DISCUSSION

We have demonstrated that influenza epidemics in Iceland were characterized by 3 major patterns over the last century. In the early 20th century, influenza exhibited irregular cycles, including epidemics with late-spring and summer peaks, and a 2-year epidemic period that occurred through the 1930s. Between 1940 and 1990, influenza activity became strongly winter-seasonal with an annual periodicity and a lag in epidemic timing of ~1 month on average as compared with that in Denmark, France, or the United States. Another shift occurred in the early 1990s, when the average lag between the epidemic peaks in Iceland and the other countries was no longer detectable by use of monthly data. The first change in timing could have been influenced by increasing population density within Iceland, by improvements to the domestic transportation systems (11), or by changes in international ocean traffic. The second change in epidemic timing, in which the

1-month lag is no longer detectable, could plausibly have been affected by increases in the volume of international tourists coming to Iceland and increased travel abroad by Icelanders.

These findings have implications for influenza pandemic planning: Of the 2 shifts in epidemic timing that we observed, the first, more dramatic shift occurred prior to the airline era when few foreigners visited Iceland each year. The second shift in timing, in which the 1-month lag was no longer detectable between the epidemics in Iceland and the other countries, might be attributable to increases in air traffic. This means that even in an isolated population with no international land connections, airline traffic can account for a shift in timing of, at most, 1 month. Efforts to close borders and restrict air travel during influenza pandemics would have a limited impact upon slowing the intercountry spread of disease in most populations in the Northern hemisphere, particularly in countries where there are multiple modes of international transit. This is consistent with a previous predictive modeling study by Hollingsworth et al. (22), which suggested that, once an epidemic is underway, closing airports might slow the spread of an epidemic to a new country but would not ultimately prevent its spread in the absence of a vaccine.

Further supporting the view that airport closures would have limited impact, the United States and Denmark showed a consistent degree of synchrony throughout the entire period, even before the era of commercial airline travel (Web Figure 4). This suggests that influenza virus might have already reached close to a peak transmission rate even given the lower population density, modes of transport, and

patterns of travel in the early 1900s. This is also in agreement with observations of the rapid global spread of the Russian flu pandemic in 1889–1890 (23). However, the Russian flu did not make it to Iceland until mid-year 1890, whereas the second wave of Spanish flu was readily transmitted from Europe to Iceland in October 1918 (24). Interestingly, attempts to halt the spread to the northern and eastern part of the island were successful, preventing almost 40% of the population from exposure to the virus (24, 25).

The effect of Iceland's early isolation on infectious disease transmission is clear from earlier work by Cliff et al. (11, 21) and by Cliff and Hagget (26) in which they demonstrate increasing similarities in measles and influenza epidemic patterns between Iceland, Europe, and North America in the period after 1945 and suggest a role for foreign military personnel in driving these patterns. This is consistent with our findings here in which the major shift in influenza epidemic timing—from irregular nonseasonal peaks to regular winter seasonality—occurred in the 1930s or 1940s. Cliff et al. (21) also demonstrate that the speed of spread of influenza within Iceland increased through the mid-1900s, which could impact the overall peak timing for the country. It appears from our analysis, however, that the lag between southwestern Iceland and the rest of the country had essentially disappeared by the early 1970s, suggesting that the speed of within-country spread had reached its plateau before epidemics became synchronous with those in other countries in the 1990s. The synchrony within Iceland is confirmed by data from the 2009 influenza pandemic when most of the country experienced the pandemic peak within 1 week of Reykjavík (27).

It is possible that the dominant influenza subtype could influence speed of spread of influenza with more synchrony in H3N2-dominant seasons (28). In turn, seasons dominated by influenza strains for which there is low herd immunity might disseminate more rapidly, resulting in smaller phase differences between countries. Our data show that periods of increased synchrony (the 1970s, 1990s, 2000s) are interspaced with periods of increased phase differences (1980s), which could potentially be explained by cycling of dominant influenza subtypes. Unfortunately, the lack of virus subtype information for Iceland precluded a more formal analysis.

Our approach has several limitations. First, we assumed that seasonal epidemics are principally the result of new introductions of the virus every winter, consistent with the circulation patterns of influenza virus in temperate areas (29). Other important determinants of epidemic timing, such as humidity (17), could help to synchronize epidemics. The variation in epidemic timing between the Northern Hemisphere and the Southern Hemisphere, where influenza epidemics occur in their respective winter seasons, underscores the important contribution of climate factors to general seasonal patterns. As suggested by recent modeling work (8), some combination of environmental conditions and seeding of the virus via international travel likely influences the observed timing of epidemics.

We also assume that epidemics that occur in different countries in the same season are caused by the same viral strain. This is not always the case: In 2003–2004, for instance, many countries had an epidemic of the H3N2/Fujian strain in late autumn, whereas Iceland had an outbreak of influenza A H1 (30). Such mismatches could account for some of the heterogeneity in timing that we are unable to explain by other factors. More detailed viral genetic and antigenic data would help to test this possibility.

Because of availability of data, we used morbidity statistics from Iceland and Denmark and mortality statistics from the United States and France. Although it would be ideal to use comparable data among all 4 countries, mortality data in Iceland are too sparse because of the small population, and morbidity data from the United States are not available for much of the time period. There is likely an additional lag of several days to 2 weeks from clinical presentation to death, which we do not control for here. However, the timing of influenza morbidity and mortality peaks is closely linked (28), and our conclusions are based on relative changes in synchrony between epidemic indicators over long time periods. These lags would only be an issue if there were considerable changes in the interval between consultation and death during the course of the study.

Another caveat is related to the use of annual tourism statistics, rather than statistics specific to the periods immediately preceding the influenza season. In recent years, the Icelandic tourism patterns have been highly seasonal, with the majority of the travelers visiting the country in midsummer (14, 31). Seasonal data from before 1989 are not available, but statistics from 1989 to 2000 suggest that the number of visitors in the autumn and spring increased at a faster rate than the number of visitors in the summer and winter (32).

In summary, we have demonstrated that the seasonal influenza patterns for Iceland have undergone 2 major transformations during the past century, whereas influenza peaks in the United States and northern Europe have been synchronous and regular during this time. An ~1-month shift in influenza timing was detected in the 1990s, during which the lag between epidemics in Iceland and the United States and Europe was no longer detectable and could be related to increases in the volume of international contacts. Given the current level of international transportation, efforts to close borders and restrict air travel during influenza pandemics would likely have a limited impact upon the spread of influenza, even for island populations.

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