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Large-Scale Comparative Analysis of Pertussis Population Dynamics: Periodicity, Synchrony, and Impact of Vaccination

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Pertussis is a worldwide infectious disease which persists despite massive vaccination campaigns that have gone on for several decades. To obtain an overall view of pertussis dynamics and the impact of vaccination, the authors performed, using the wavelet method, a comparative analysis of pertussis time series in 12 countries to detect and quantify periodicity and synchrony between them. Results showed a clear 3- to 4-year cycle in all countries, but the main finding was that this periodicity was transient. No global pattern in the effect of vaccination on pertussis dynamics was observed, but some spatial synchrony between countries was detected. This large-scale comparative analysis of pertussis dynamics sheds light on the complexity of the multiple interactions involved in global pertussis spatial dynamic patterns. It suggests a need to perform a global survey of human infectious diseases over the long term, which would permit better assessment of the risk of disease outbreaks in the future.

comparative analysis; periodicity; population surveillance; vaccination; wavelet methods; whooping cough

Recent insights into the population biology of infectious diseases have clearly shown the importance of associating empirical studies with theoretical studies in order to better understand the causes of disease transmission, thereby enabling better control of their impact on human health (1–5). In a recent paper issued after a multidisciplinary workshop on pertussis that brought together scientists and physicians from different disciplines, van Boven et al. (6) pointed out the main drawbacks of current epidemiologic studies. As van Boven et al. (6) noted, one resolution made at the workshop was to develop comparative analysis of both data and model outputs to obtain a complete picture of disease behavior in both space and time. A promising approach lies in comparing a long-term series of disease cases across localities and countries so as to characterize variations in the pre- and postvaccine periods and determine the existence of synchrony between time series. Such an approach should considerably improve our understanding of trends in global disease dynamics and thus facilitate the emergence of predictive and quantitative tools for vaccination programs.

Although there have recently been major research developments in other fields of life science (i.e., population dynamics, community ecology, and macroecology (7)), often through the use of a comparative research perspective, epidemiology continues to suffer from a lack of comparative studies. In ecology, time-series analyses are highly developed in the study of animal population dynamics and have enabled the study of spatial synchrony between animal populations (8, 9) and the periodicity of population dynamics with geographic gradients (7). A direct application of this approach concerns conservation biology (10). For a given species, synchrony between different populations in different geographic locations (i.e., populations' being in the same dynamic state simultaneously) increases the risk of extinction. In contrast, if population dynamics

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are desynchronized, the extinction of one local population can be balanced by recolonization from a neighboring population (i.e., the rescue effect), thus allowing the species to persist regionally. Research in the field of infectious disease ecology has suggested that the same argument might be applied to human disease using both analyses of extended time series of infectious disease data (11–14) and mathematical modeling (1, 15–17). It is easier to control a disease—through vaccination, for instance—if epidemics are regular and synchronous in space (e.g., if an epidemic peaks in all populations simultaneously). In contrast, if epidemics are irregular or desynchronized in space, disease extinction in one locality will probably be temporary, since disease can be reintroduced through new cases from "neighboring epidemics." Thus, this new epidemiology will be essential for better understanding the evolution of disease behavior in space and time and will be important in terms of disease control. Finally, to gain access to a whole picture of disease evolution in term of dynamics, it is crucial to compare different environmental and demographic conditions.

Indeed, the periodicity of infectious disease dynamics has already been described for different countries, but in separate studies involving measles (4, 12, 13), pertussis (12, 14, 18), smallpox (11), and scarlet fever (1). Some studies have also focused on epidemic synchrony between cities and/or regions (4, 19, 20) in the same country or island. However, to our knowledge, no study has compared the temporal dynamics of a given disease on a large scale, that is, across countries. We undertook to conduct a comparative analysis of a pertussis time series in 12 different countries.

Pertussis, also called whooping cough, is a worldwide infectious disease that mainly affects children. Despite large-scale vaccination programs that have been ongoing for more than 50 years in developed countries, pertussis remains endemic, with recurrent outbreaks throughout the world. Developing countries generally started vaccination during the 1980s, but vaccine coverage remains dispersed and insufficient. In several countries in which vaccination coverage has been maintained at a high level, such as France (21), Canada (22), and the United States (23), a resurgence of pertussis has been clearly noted. In the context of persistence or resurgence of the disease despite vaccination programs, assessment of the overall picture of pertussis dynamics throughout the world would be helpful in understanding the global effects of vaccination.

It is generally admitted that pertussis epidemics occur every 3–5 years in many countries, but this periodicity has been clearly demonstrated for only a limited range of countries: Portugal (24), the United States (18), the United Kingdom (England and Wales) (4, 12), and a small rural area in Senegal (25). Gomes et al. (24) detected a 3.5- to 4-year cycle during the prevaccination period (1952–1962) in Portugal, whereas no indication of long-term periodicity was observed during the postvaccination period (1963–1994). Rohani et al. (4) reported, for England and Wales, an increase in the interepidemic period from 2.5 years before vaccination (1944–1957) to 3.5 years in the postvaccine era (1958–1974). In the United States, Hethcote (18) suggested that the interepidemic period was unchanged by vaccination and was approximately 4 years. A clear 3.5-year cycle was detected after vaccination in the small rural area of Senegal (25).

Spurred by previous findings, we sought to carry out a comparative analysis using a larger set of time-series data for pertussis in order to detect and quantify global pertussis dynamics in 12 countries around the world and to show the existence, or lack, of a global trend in disease dynamics and the impact of vaccination over time. We conclude with a discussion of the main perspectives that emerged from our study and the need to perform more comparative analyses in epidemiology.

MATERIALS AND METHODS

Data

This work was based on both annual (for 12 countries) and monthly (for five countries) pertussis notifications. Data were obtained from diverse sources: published graphs and tables (for Denmark (26), France (27), the United States (websites), the United Kingdom (England and Wales) (28), and Canada (22)); the authors or investigators (Portugal (24), Japan, Switzerland, and Italy); the World Health Organization (Israel and Brazil (websites)); and official public health websites (Algeria). We also possessed data from the small community in Senegal (25), but the time range (15 years) was too short for wavelet analysis with annual data, so we decided not to incorporate these data into the present analysis. The five countries for which monthly data were also available were Israel, Italy, Portugal, Switzerland, and the United Kingdom (England and Wales). The calendar periods of the time-series data and the first years of mass vaccination are shown in table 1. We obtained data for both the prevaccination period and the postvaccination period for six countries: the United States, the United Kingdom (England and Wales), Canada, Denmark, Portugal, and France. For the six remaining countries, we obtained data for the postvaccination period only. Complete data on the time series are available from the corresponding author upon request.

Periodicity—wavelet analysis

Fourier analysis has traditionally been used to analyze relations between oscillating time series. Fourier analysis decomposes time series into their different periodic components, and these periodic components can then be compared from one series to the next. This method is not always appropriate when dealing with complex population time series, since it cannot take into account the often-observed changes in the periodic behavior of such series (i.e., their lack of stationarity). We therefore used wavelet analysis (13, 29), which is well suited to the exploration of local variations in frequency (and periodicity) as time progresses. In addition to extracting the information on the different periodic components of a time series, wavelet analysis indicates the evolution of these periodic components through time (29). It is particularly well adapted to the context of our study, since it allowed us to determine whether periodic components of our series changed before and after vaccination or as a function of vaccine coverage. Prior to wavelet

TABLE 1. Details on annual pertussis time series (pertussis notifications) for 12 countries

Country	Figure and section	Data range	Year of start-up of mass vaccination*	Duration (years) of prevaccination period	Duration (years) of postvaccination period
Denmark	Figure 1, part A	1901–1997	1961	61	36
United States	Figure 1, part B	1922–2000	1940s		
Canada	Figure 1, part C	1924–1995	1943	20	52
United Kingdom† (England and Wales)	Figure 1, part D	1940–2000	1957	18	43
	Figure 2, part C	1967–1991†			24†
France	Figure 1, part E	1945–1985	1959	15	26
Portugal†	Figure 1, part F	1952–1999	1966	15	33
	Figure 2, part B	1952–1999†		15†	33†
Switzerland†	Figure 1, part G	1943–1973	1940s		31
	Figure 2, part A	1943–1973†			31†
Japan	Figure 1, part H	1947–1998	1947		51
Italy†	Figure 1, part I	1976–1996	1950s		21
	Figure 2, part D	1976–1996†			21†
Brazil	Figure 1, part J	1980–2001	1980s		22
Israel†	Figure 1, part K	1974–2000	1956		27
	Figure 2, part E	1974–2000†			27†
Algeria	Figure 1, part L	1980–2000	1980s		20

* Last year of the prevaccination period.

† Countries and periods for which monthly data were also obtained.

analyses, the data for all series were square-root-transformed in order to dampen extremes in variability. In addition, we estimated all oscillating components with a period greater than half of the time-series length using a high-pass Gaussian filter, and we detrended series by subtracting these oscillating components. More technical details on wavelet analysis are given in the Electronic Appendix (available on the *Journal*'s website (www.aje.oupjournals.org)).

Coherence and synchrony analyses

Coherence is similar to some classical correlation, but it pertains to the oscillating components in a given frequency mode. Wavelet coherence generalizes the possibilities of wavelets for quantifying the dependencies between two signals. These tools allow us to quantify the synchrony of two time series in a given periodic mode—that is, to quantify whether two time series tend to oscillate simultaneously, rising and falling together with the same period. In complement to wavelet analysis, we can use phase analysis (30) to characterize the association between signals (13) and compute the instantaneous time lag between the time series (see Electronic Appendix).

Comparative analysis

The comparative approach, already developed in macroecology (31), consists, in our case, of analyzing a set of time-series data on the same disease across several countries (i.e., on a large scale) to try to detect and quantify global dynamics and synchrony patterns.

RESULTS

Periodicity

Annual data. All annual time-series data (square-root-transformed) are represented in the left panel of figure 1, and results from the wavelet spectrum and mean spectral analyses are illustrated in the middle and right panels, respectively. First, we focused on the six countries for which both pre- and postvaccination data were available (Denmark, the United States, Canada, the United Kingdom (England and Wales), France, and Portugal). Periodicities were detected during both periods in all countries, even if they did not last throughout the whole time period, except for Canada and Portugal. For Denmark (figure 1, part A), where mass vaccination started in 1961, an approximate 3-year cycle was detected between 1918 and 1925, and then an increasing period from approximately 3.5 years to 4.5 years was clearly shown from the second half of the 1940s to around 1967. After this, no clear periodicity was detected. For the United States (figure 1, part B), a 4-year period was shown during the 1930s that also lasted until around 1967, despite mass vaccination starting in the mid-1940s. Canada (figure 1, part C) did not show any periodicity before

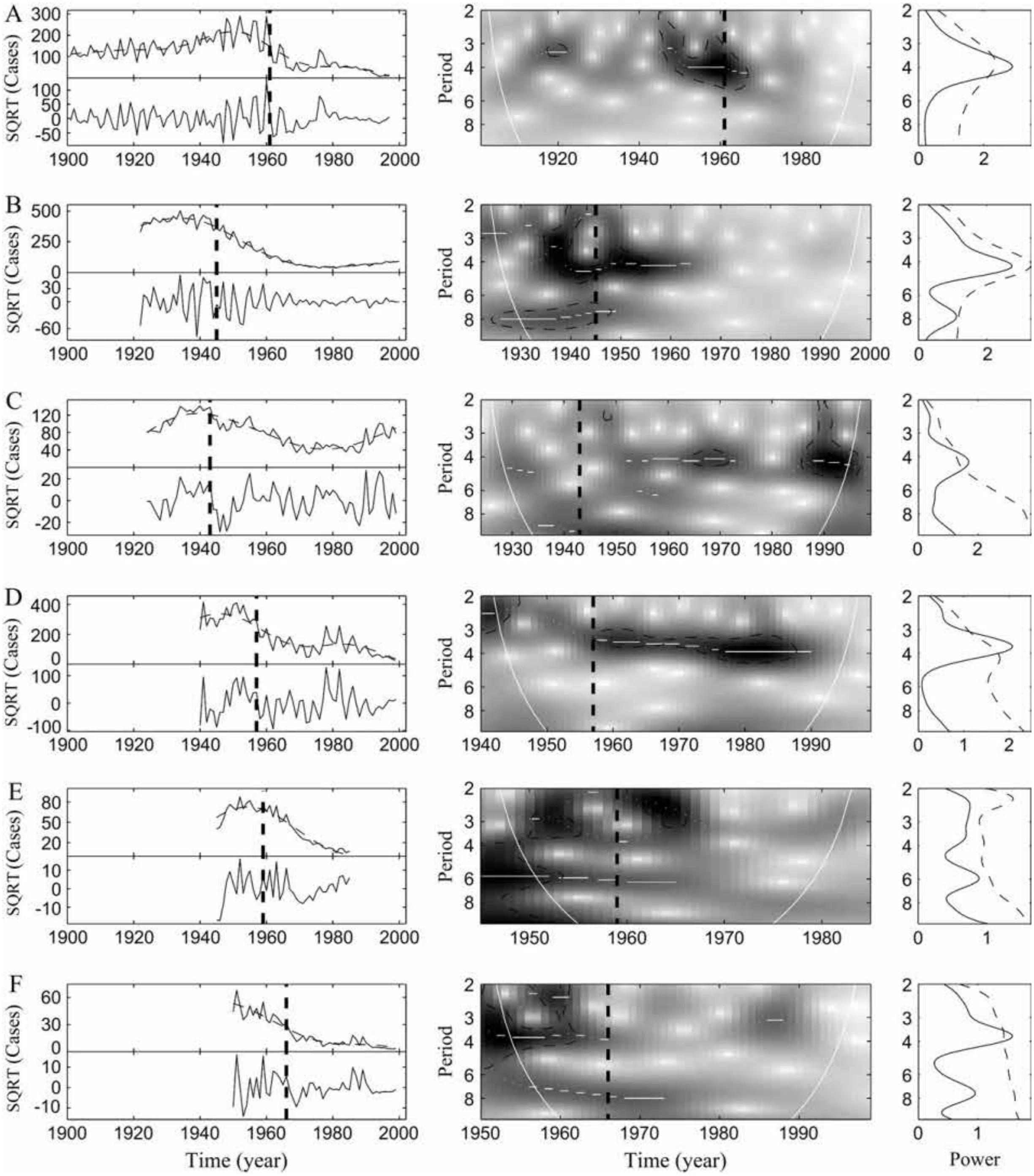

Figure 1 continues

vaccination, whereas a 4-year cycle was detected during the postvaccination period. The United Kingdom (figure 1, part D) showed increasing periodicity after vaccination, with the start of mass vaccination in 1957; a 2.5-year cycle was detected before vaccination and then increased to a 3.5- to 4-year period after vaccination. In France (figure 1, part E), where massive vaccination began in 1959, an approximate 2.5- to 3-year cycle was observed in the first half of the 1950s and then during the 1960s until 1967; after that, no periodicity emerged. In contrast, Portugal (figure 1, part F)

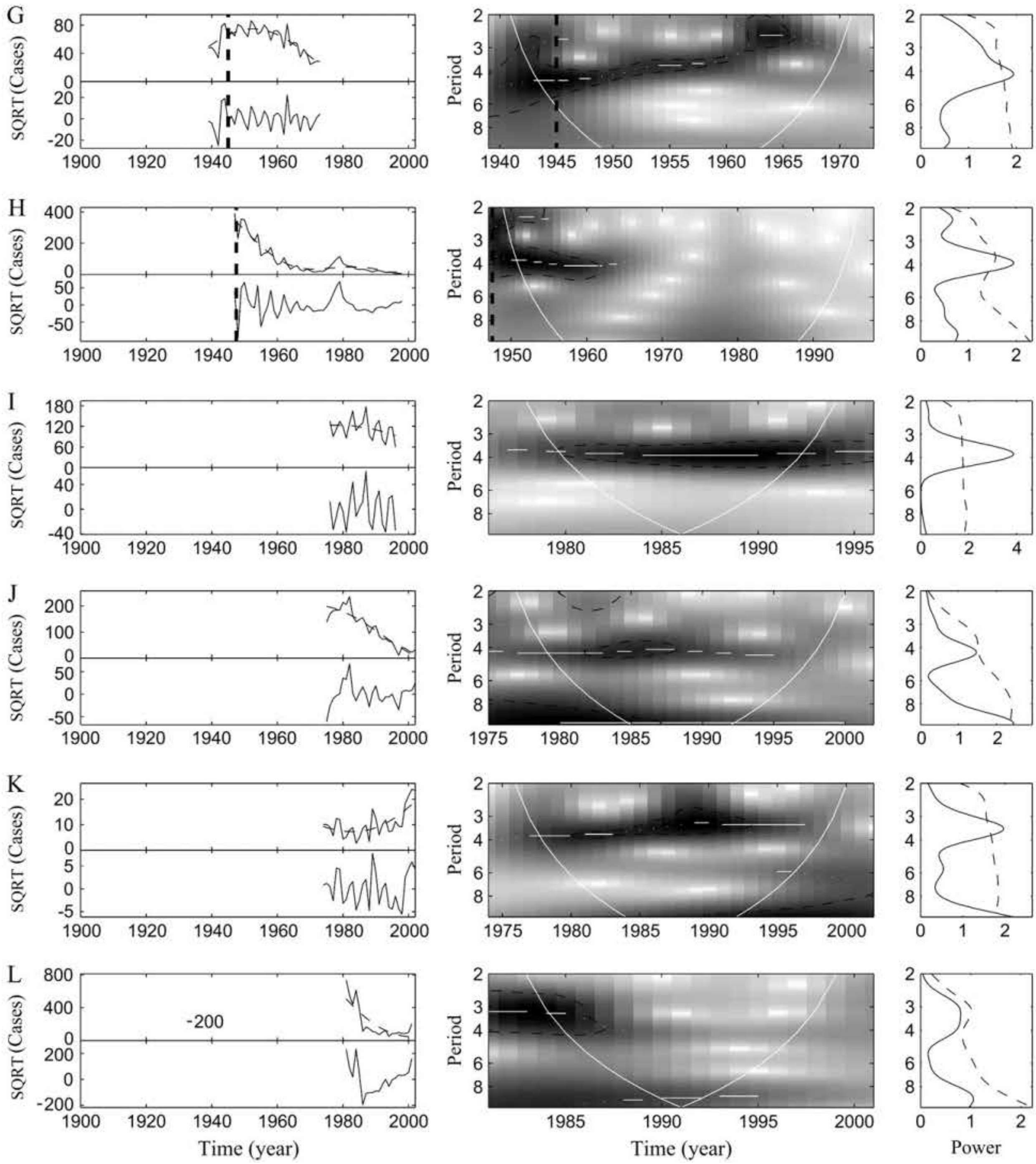

Figure 1 (continued)

FIGURE 1. Wavelet analyses of pertussis time series with annual data across 12 countries: (A) Denmark, (B) the United States, (C) Canada, (D) the United Kingdom (England and Wales), (E) France, (F) Portugal, (G) Switzerland, (H) Japan, (I) Italy, (J) Brazil, (K) Israel, and (L) Algeria. For each country, the left panel shows the time series. The top graph corresponds to the square-root (SQRT)-transformed data and their trend line; the bottom graph illustrates the detrended time series. The dashed vertical lines indicate the year of the start of mass vaccination in that country (also see middle panel). The middle panel shows the wavelet power spectrum of pertussis cases (detrended) (*x*-axis: year; *y*-axis: period, in years). The shading represents increasing spectrum intensity, from white to black; the dotted black curves show the statistically significant area (threshold of 5% confidence interval); and the white curve delimits the cone of influence (region not influenced by edge effects). Finally, the right panel corresponds to the mean spectrum (black line) with its significant threshold value of 5% (dotted line). For homogenization of the overall presentation, the time series illustrated in the left panels are for 1900–2000, but wavelet spectra in the middle panels show the specific data range of each country.

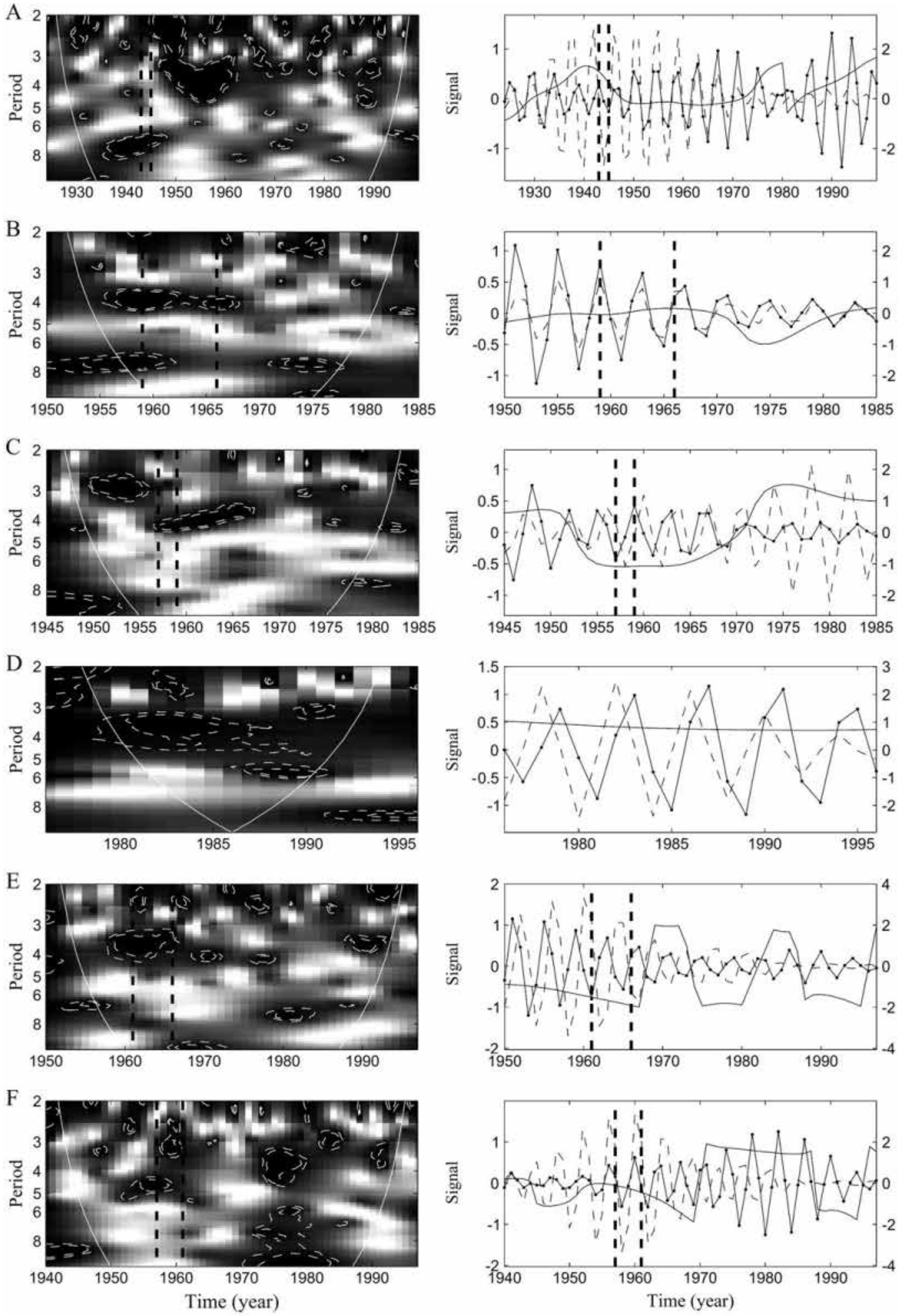

FIGURE 2. Wavelet coherence and synchrony analyses of pertussis time series between countries. The left panel shows wavelet coherence (*x*-axis: year; *y*-axis: period, in years), with white representing low coherence and black representing high coherence. The dotted black curves show the areas of 5% and 10% statistical significance ($\alpha = 5\%$ and $\alpha = 10\%$) based on 500 bootstrapped series. The cone of influence (white curve) indicates the region not influenced by edge effects. The right panel shows the oscillation components of two epidemiologic time series computed, based on wavelets, in the 3.5- to 4.2-year periodic band: (A) United States/Canada; (B) France/Portugal; (C) United Kingdom (England and Wales)/France; (D) United Kingdom/Italy; (E) Denmark/Portugal; (F) Denmark/United Kingdom. Dashed lines: first country; solid lines with dots: second country; solid lines without dots: time delay between the two oscillating components (ΔT).

showed an approximate 4-year period before vaccination and no periodicity after vaccination.

Examination of the six other countries for which only postvaccination data were available indicated that all countries showed more-or-less regular periodicities: Switzerland (figure 1, part G) showed decreasing periodicity from approximately 4 years in the 1950s to approximately 2.5 years in the 1960s; Japan (figure 1, part H) had a clear 4-year period from 1945 to the beginning of the 1960s; Italy (figure 1, part I) showed a clear 4-year period during the entire period under study; an approximate 4-year cycle during the 1980s was detected for Brazil (figure 1, part J), but this trend was not observed during the entire period; a global 3.5-year cycle was shown in Israel (figure 1, part K); and finally, Algeria showed a 3-year cycle during the 1980s but no periodicity from 1990 to the present (figure 1, part L).

Monthly data. Monthly time-series data and corresponding analyses are illustrated in Web figure 1, which is posted on the *Journal*'s website (www.aje.oupjournals.org). All of these analyses confirmed findings obtained with annual data. Moreover, no annual periodicity was detected for the different series, except during the prevaccination period in Portugal (i.e., 1956–1966).

Coherence and synchrony analyses

Results for coherence and the main oscillating components are presented in figure 2 (left and right panels, respectively). Wavelet coherence of pairwise comparisons reveals only a discontinuous association between the dynamics of the different countries. Nevertheless, the majority of these associations are in the 3- to 4-year periodic band.

Synchrony was observed between the United States and Canada from 1924 to 1970 (figure 2, part A), which corresponds to both prevaccination and postvaccination periods. Nevertheless, a delay of 1 year seemed to appear starting in the 1970s. In Europe, no global synchrony was observed. France and Portugal were globally synchronous (figure 2, part B) during the entire common period (i.e., 1950–1985). France started mass vaccination in 1959 and Portugal in 1966, and thus synchrony was not disturbed by vaccination. The United Kingdom (England and Wales) and France were synchronous but out of phase (1–2 years) between 1950 and 2000, that is, before and after mass vaccination in both countries (figure 2, part C). The United Kingdom and Italy were also synchronous but out of phase (1 year) during the postvaccination era, that is, between 1976 and 1996 (figure 2, part D). In contrast, all other pairwise comparisons showed changes in dynamics. For instance, Denmark and Portugal (figure 2, part E) showed a delay of 1 year before vaccination (1950–1961), while a delay of 2 years was detected after vaccination in both countries (1967–1995). Denmark and the United Kingdom (figure 2, part F) were slightly synchronous before mass vaccination started in the two countries (1940–1957), whereas a delay of approximately 2 years was shown when both countries began vaccination (1962–1995). In contrast, the United Kingdom and Portugal showed a delay of 1 year before vaccination (1950–1966), and then the two dynamics became synchronous in time between 1967 and 1995 (see figure 2, part G; the second half of figure 2 appears as ''Web figure 2'' on the *Journal*'s website (www.aje.oupjournals.org)).

We did not obtain sufficient data to analyze both pre- and postvaccination periods between North America and Europe; the common data range did not overlap sufficiently that we had access to a time period in which one of the two countries (but not the other) was vaccinated and then a time period in which both countries were vaccinated. Global results showed a delay of 1 or 2 years between Europe and North America during the vaccine era. For instance, the United States and Switzerland (figure 2 (i.e., Web figure 2), part H) and the United States and France (Web figure 2, part I) were synchronous but out of phase by 1–2 years between the 1940s and the 1970s and between 1945 and 1985, respectively. Japan was out of phase by 1 year with the United States (Web figure 2, part J) and Canada (not shown). Japan was also out of phase by 1 or 2 years with Europe—for instance, with Portugal (Web figure 2, part K), the United Kingdom (Web figure 2, part G), and France (not shown). Algeria was synchronous but out of phase (2 years) with Brazil (not shown) and Europe (as, for instance, with Italy) (Web figure 2, part L). Finally, Israel appeared to be out of phase by approximately 1 or 2 years with the United Kingdom (Web figure 2, part M).

Overall, no clear trend in spatial synchrony was observed across countries, whereas we did observe a clear 3- to 4-year periodicity.

DISCUSSION

Periodic patterns of infectious disease dynamics have been previously described and/or modeled for scarlet fever (1), smallpox (11), and measles (12, 32). Modern epidemiology is now confronted with the problem of how to identify the spatiotemporal and organizational scales that might be relevant in explaining disease patterns and processes. Many investigations on childhood diseases have also provided clear evidence of how large-scale studies are of substantial interest for public health (14, 20, 33). Therefore, a fully quantitative understanding of disease patterns in time requires empirical comparative studies that are currently dramatically lacking in epidemiology. This approach, called ''comparative analysis,'' consists of the comparison, on a broad spatial scale, of long-term data for a given disease across different localities, as illustrated in this work.

Taking advantage of population time series for pertussis cases across 12 different countries for which annual data were available, we performed a large-scale comparative analysis of pertussis dynamics—to our knowledge, the first such analysis. Although heterogeneity in the data due to the use of various information sources and differing survey methods across countries may have interfered with our findings, a periodicity of approximately 3–4 years was detected in all 12 countries. Similar results were obtained for pertussis dynamics in the small community in Senegal (25).

Based on the analysis of 12 time series of reported cases, our major finding was that this periodicity is transient and nonuniform across countries. Indeed, this 3- to 4-year periodicity was rarely present during the entire time range of each country's time series. These detectable differences in disease periodicity variation with time are due to the use of wavelet techniques capable of capturing the actual tendency toward cycles at any given time, and this represents the major advantage of this method over all other classical statistical and mathematical tools. For the subset of five countries for which monthly data were also available, wavelet analyses gave results similar to those obtained with annual data, suggesting that major patterns in disease population dynamics were captured by annual time series as well.

However, no global pattern was observed either before or after vaccination or in periodicity modification due to vaccination. In particular, the absence of global synchrony between countries allows us to reject the hypothesis of the existence of a common external force explaining periodicity. Indeed, an external force (e.g., climatic factors) should synchronize all dynamics; this phenomenon is called the Moran effect (34). Moreover, the tendency toward an increase in periodicity during the postvaccine era, as demonstrated for the United Kingdom (4, 14), was not detected for other available countries, suggesting that no generalities can be made without carrying out a broad-scale analysis.

In addition, countries could not be grouped according to their vaccine history (i.e., vaccine coverage, type of vaccine used, arrest of vaccination, or variation in cyclicity of the disease time series). Indeed, the 3- to 4-year periodicity trend in pertussis population dynamics across countries was remarkably well-observed under different vaccine conditions (i.e., no vaccination, constant high vaccination (e.g., Canada, France, the United States), lower vaccine coverage (e.g., Denmark, Italy), irregular vaccination coverage in time (e.g., Japan, United Kingdom), or different types of vaccines used in time (e.g., Japan, Canada)), which indicates that vaccine history parameters were not influential in these cyclic disease population dynamics. Infectious disease cycles are usually explained by demographic parameters characterizing the amount of time necessary for the development of a sufficiently susceptible pool to allow the epidemic to start (33). Nevertheless, such a common 3- to 4-year cycle, as observed in countries with different sociodemographic conditions (e.g., the United States and Algeria), implies that these factors, like vaccination, are not the main determinants of pertussis dynamics but, rather, intrinsic pathogenic parameters may intervene in disease dynamics.

Many of these discrepancies in findings could be explained by the complexity of interactions between vaccination, sociodemographic conditions, and external factors influencing disease dynamics, such as transcontinental air travel and globalization, which place into contact human communities that were previously isolated from one another. Topography and human settlement patterns may also affect global pertussis dynamics, as observed with two neighboring countries having important travel and trade exchanges and showing synchronous time series when compared with two distant countries (see Morens et al. (35) and Cohen (36) for reviews). Data heterogeneity could also explain such observed differences in periodicity. Indeed, pertussis surveillance is not performed with common recommendations across the countries we studied here.

This comparative approach to infectious disease dynamics has shed light on the complexity and fluctuating state of disease population dynamics and the importance of assessing the overall view of infectious disease behavior to enable more effective disease control. Comparative analysis is a promising approach to public health concerns in infectious disease population dynamics, in that it offers a much broader perspective on health and a more quantitative approach to predicting and controlling disease evolution. In a world of increasing exchanges between countries and thus between pathogen populations, a global, standardized survey of infectious disease is highly recommended. Public health investigators should incorporate such research strategies in the near future as long-term data on diseases become more abundant.

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