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Influenza Pandemics in Japan during the 20th Century

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ABSTRACT

Objectives : We aimed to elucidate factors associated with variations in the excess death rate (EDR) within prefectures with influenza pandemics.

Methods : Monthly deaths from influenza, pneumonia, and all causes were abstracted from vital statistics from 1899 to 2006. The EDR due to all causes (AC-EDR) and the EDR due to pneumonia or influenza (PI-EDR) were then calculated in 47 prefectures.

Results : For death rates, 2 prominent peaks were associated with the Spanish flu, but no peaks occurred for the 1957 Asian flu or the 1968 Hong Kong flu. The excess deaths due to all causes and due to pneumonia or influenza from 1918 to 1920 were 577,115 and 444,305, respectively. The death rate was increased in persons aged 25 to 30 years. Prefectures with higher EDRs around the first peak tended to have a lower EDR around the second peak, and vice versa. The AC-EDR and PI-EDR for 3 years differed by 13.6 times and 1.9 times, respectively, within prefectures ; 32% of this variability was attributed to the higher illegitimate/legitimate birth ratio, lower population density, and the higher death rate of 1-year-olds in 1917.

Conclusions : These results suggest that improving the quality of community health and regional socioeconomic variables in peacetime may be key issues in reducing deaths during an influenza pandemic. (Jikeikai Med J 2010 ; 57 : 89-99)

Key words : influenza, pandemic, Spanish flu, Asian flu, Hong-Kong flu

INTRODUCTION

Two influenza pandemics appear to have occurred in the 18th century (1729-1733 and 1781-1782), 2 occurred in the 19th century (1830-1833 and 1889-1892), and 3 occurred in the 20th century. Influenza pandemics in the 20th century included the Spanish flu : H1N1[1] from 1918 to 1920 ; the Asian flu : H2N2[2] in 1957 and 1958 ; and the Hong Kong flu : H3N2[3] in 1968 and 1969. In addition to historical pandemics of influenza, there were 2 pseudopandemics : 1 in 1947, which was associated with low death rates, and 1 in 1977, which occurred among children[4]. Forty years have passed since the last major pandemic. Moreover, new types of H5N1 avian influenza emerged in 1997 and spread around the world after 2003[5]. If the H5N1 avian influenza develops sustained human-to-human transmissibility, it could trigger an influenza pandemic similar to the Spanish flu[6]. Thus, the next influenza pandemic is now a global concern.

Of the different flu viruses, the one causing the Spanish flu is the most notorious and resulted in approximately 50 million deaths worldwide[7]. However, even without vaccination and antiviral drugs, many people recovered from this infectious disease during the Spanish flu pandemic. Understanding how they overcame the Spanish flu may help us prepare for a future pandemic. A recent census report of 43

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cities in the United States suggests that early, sustained, and layered application of nonpharmaceutical interventions, such as school closures, cancellation of public gatherings, and isolation or quarantine of infected and exposed individuals, might delay the time to peak mortality and lower the peak mortality and total mortality rates[8,9]. Another recent study has examined high-quality vital registration data and has found that per-capita income might explain half of the variability in death rates across countries during the Spanish flu pandemic[10]. Likewise, socioeconomic factors, measured with city-specific per-capita data, played a role in the excess mortality before the Spanish flu pandemic[11]. These findings are extremely important in establishing a strategy to prepare for the next influenza pandemic. In addition, we should learn more not only from the Spanish flu[12,13] but from other pandemics as well[14].

Japanese vital statistics have been available since 1899, excluding the period of the Second World War. Crude death numbers and rates, stratified by cause of death, month, and prefecture, can also be retrieved. We explored long-term trends in deaths due to pneumonia or influenza over more than 100 years and focused on the excess death rate (EDR) during the Spanish flu pandemic from 1918 to 1920 to elucidate factors that can explain the variability of EDR within the 47 prefectures.

METHODS

Data collection

Monthly mortality data from influenza, pneumonia, and all causes were abstracted from vital statistics of Japan[15] from 1899 to 2006, except for 6 years during and after the Second World War. Thus, 102 years of data were assessed. First, monthly crude vital statistics of all-cause death rates/100,000 persons (AC-DR), pneumonia plus influenza death rates/100,000 persons (PI-DR), and influenza death rates/100,000 persons (I-DR) were used. Then, the all-cause EDR/100,000 persons (AC-EDR) and the pneumonia plus influenza EDR/100,000 persons (PI-EDR) were calculated by subtracting the corresponding median death rates of the same calendar month and the same prefecture during parapandemic periods in 1915, 1916, 1917, 1921, and 1922 from monthly death rates in each prefecture during the Spanish flu pandemic period of 1918 to 1920. Because an estimated 142,800 people are thought to have died because of the Great Kanto Earthquake on September 1, 1923, to calculate the EDR we excluded vital data from 1923. Finally, the maximum growth rate, calculated by the formula below, the peak AC-EDR/PI-EDR ratio, and the sum of the AC-EDR/PI-EDR ratios were calculated and stratified by the first 18 months of the Spanish flu pandemic (January 1918 to June 1919), which included the first peak of death observed in November 1918, and the second 18 months of the Spanish flu pandemic (July 1919 to December 1920), which included the second peak of deaths in January 1920. In addition, PI-EDR and AC-EDR were totaled during the 3 years of the Spanish flu pandemic from January 1918 through December 1920.

$$\text{Growth rate(r)} = \frac{1}{t_2 - t_1} \text{Ln}\left(\frac{I(t_2)}{I(t_1)}\right) / \text{month}$$

Where t_1 = certain month, t_2 = next month, I = number of deaths due to influenza or pneumonia, and Ln = natural logarithm.

We also referred to a summary report published in 1922 by the Japanese Home Office during the influenza pandemic in Japan and throughout the world[16]. This report included data on the mortality and morbidity due to influenza. Moreover, the timing and the number of school and factory closures and other preventive measures were listed for each prefecture. In addition, signs and symptoms and the onset and course of influenza, pathological changes including complications, and the effects of treatment and preventive measures were provided. However, it should be noted that patients with the flu during the pandemic might not have visited a physician's office, the diagnoses might be not have been as accurate as in the present day, and no information was available about the total number of schools and factories in each prefecture. Moreover, schools and factories might have been closed because of high morbidity and mortality rates as well as to prevent disease spread. Therefore, we referred to, but did not use, these data

in our results.

From the vital statistics of Japan, we abstracted the following data for each prefecture in 1917: population and population density in November 1917, birth rate/1,000 population, illegitimate/legitimate birth ratio, stillbirth rate/1,000 population, marriage rate/1,000 population, divorce rate/1,000 population, total death rate/1,000 population, death rate of newborns (0–28 days)/1,000 population, death rate of infants (1–12 months)/1,000 population, and death rate of each age group/1,000 population (1 year, 2 years, 3 years, 4 years, 5–10 years, 10–15 years, 15–20 years, 20–25 years, 25–30 years, 30–35 years, 35–40 years, 40–45 years, 45–50 years, 50–55 years, 55–60 years, 60–65 years, 65–70 years, 70–75 years, 75–80 years, 80–85 years, 85–90 years, and 90–95 years).

Statistical analysis

We used the software program Stata version 9.1 for statistical analysis (StataCorp LP, College Station, TX, USA). The Wilcoxon signed-rank test was used to compare outcomes in each prefecture between the first and second waves. Multiple linear regression models were applied to explain the variability of the EDR in the 47 prefectures. To determine factors and fix the final multiple linear regression models of the AC-EDR and PI-EDR, the stepwise backward elimination method with the factors listed above was used with a cutoff point of $P=0.2$. This cutoff point was set lower than the ordinal cutoff point of $P=0.05$ to avoid type I errors.

Results

Epidemic curves of monthly death rates/100,000 population since 1899

First, we examined monthly crude, long-term death rates/100,000 population/month for the AC-DRs, PI-DRs and I-DRs in Japan from 1899 to 2006 (Fig. 1A). Two prominent spikes representing the Spanish flu in 1918/1919 and in 1919/1920 occurred for all 3 epidemic curves. In contrast, a spike from the Great Kanto Earthquake in 1923 was recognizable only in the AC-DR but not in the PI-DR or I-DR, as we had expected. The AC-DR and PI-DR steadily decreased after the Great Kanto Earthquake until the

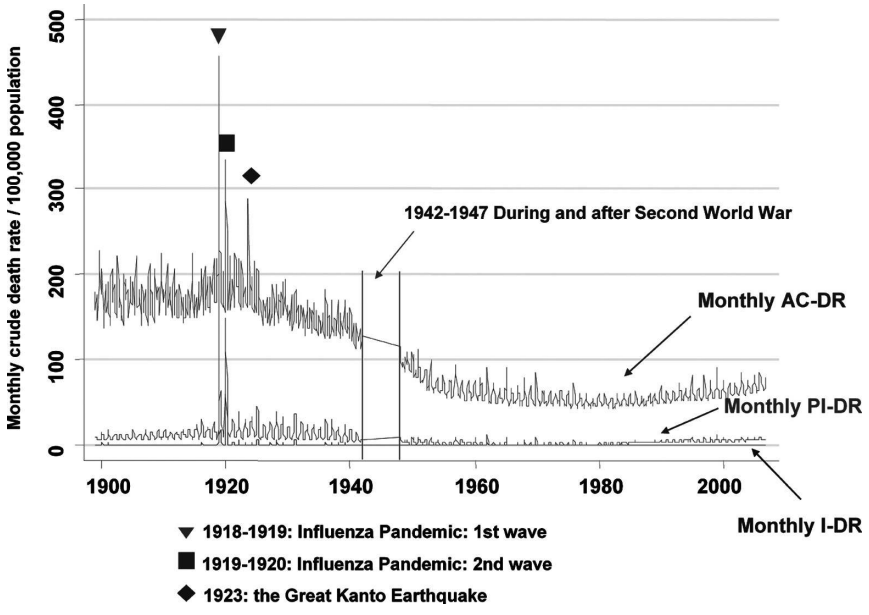

Fig. 1A Epidemic curves of monthly all causes death rate/100,000 (AC-DR), pneumonia plus influenza death rate/100,000 (PI-DR) and influenza death rate/100,000 (I-DR) from 1899 to 2006. Triangle arrow indicates 1st wave of influenza pandemic peaked in November 1918. Square arrow indicates 2nd wave of influenza pandemic peaked in January 1920. Diamond arrow indicates the Great Kanto Earthquake at September 1923. Enough data between 1942 and 1947 were not obtained because of Second World War.

1980s, but in the past 20 years, the AC-DR and PI-DR have gradually increased.

When focusing only on the PI-DR and I-DR, there were no prominent peaks around the 1957 Asian flu pandemic or around the 1968 Hong Kong flu pandemic (Fig. 1B). Further to enhance the hazardous effects of these 2 pandemics in 1957 and 1968 in Japan, we graphed the I-DR/AC-DR ratio (Fig. 1C) and the PI-DR/AC-DR ratio (Fig. 1D). Peaks were still not obvious for either the Asian flu or the Hong Kong flu.

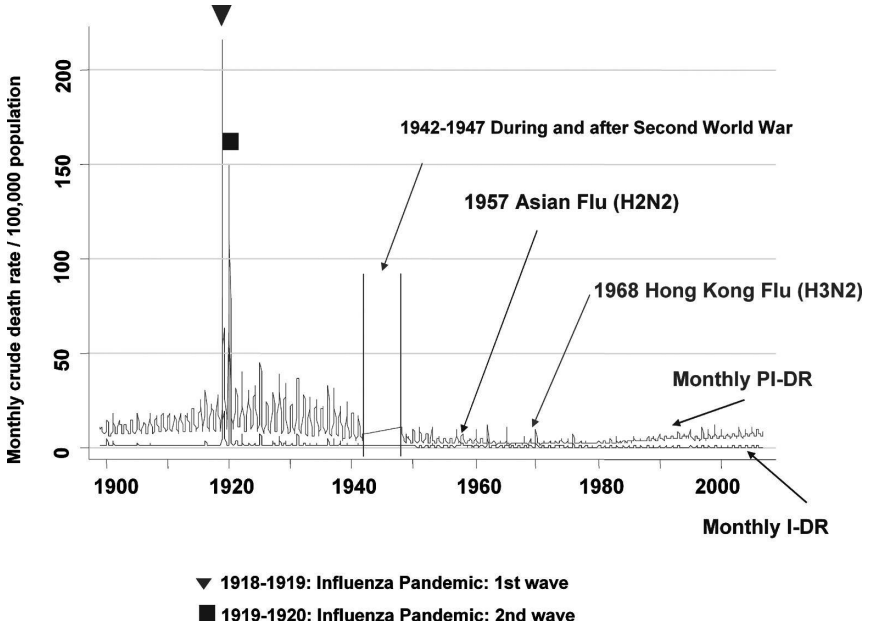

Fig. 1B. Epidemic curves of monthly pneumonia plus influenza death rates/100,000 population (PI-DR) and influenza death rates/100,000 population (I-DR). The triangle arrow indicates the first wave of the influenza pandemic, which peaked in November 1918. The square arrow indicates the second wave of the influenza pandemic, which peaked in January 1920. The timing of the Asian flu (1957) and Hong Kong flu (1968) are also indicated in the graph.

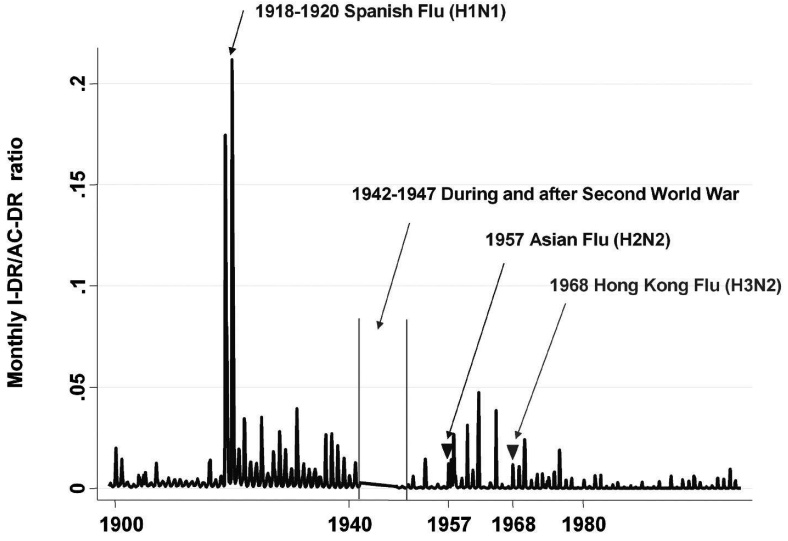

Fig. 1C. Epidemic curves using the ratio of the monthly influenza death rate (I-DR) to the all-cause death rate (AC-DR) for the same month. The timing of the Spanish flu (1918-1920), Asian flu (1957), and Hong Kong flu (1968) are also indicated in the graph.

In the I-DR/AC-DR ratio (Fig. 1C), before the Spanish flu, the amplitude of annual oscillations was small but the cycle was regular, and several spikes were recognized. After the Spanish flu pandemic period, the amplitude of oscillations was increased. After the Second World War, annual oscillations were less clear, but spikes were repeated irregularly. However, after 1980 the I-DR/AC-DR ratio stabilized at a lower level with occasional small spikes. Similar tendencies were observed for the PI-DR/AC-DR ratio (Fig. 1D). However, the PI-DR/AC-DR ratio started to increase after the 1970s. A dip was observed in 1995 owing to the transition from the 9th to the 10th International Statistical Classification of Diseases and Related Health Problems, which might have affected the diagnostic criteria for pneumonia.

Trends of the PI-DR were also analyzed while focusing on shorter periods around influenza pandemics from 1899 to 1940 (Fig. 1E). The amplitude of annual oscillations was small before the 1918 Spanish flu pandemic but gradually increased over time. In contrast, after 1920, the amplitude of annual oscilla-

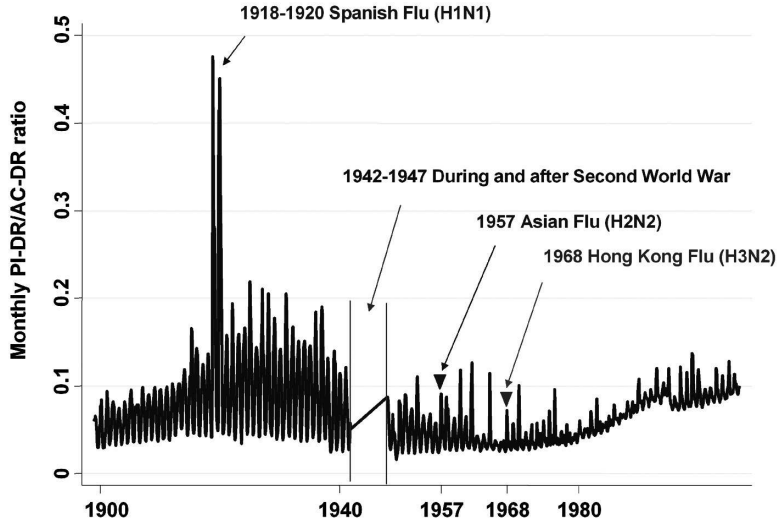

Fig. 1D. Epidemic curves using the ratio of the monthly pneumonia and influenza death rate (PI-DR) to the all-cause death rate (AC-DR) for the same month. The timing of the Spanish flu (1918-1920), Asian flu (1957), and Hong Kong flu (1968) are also indicated in the graph.

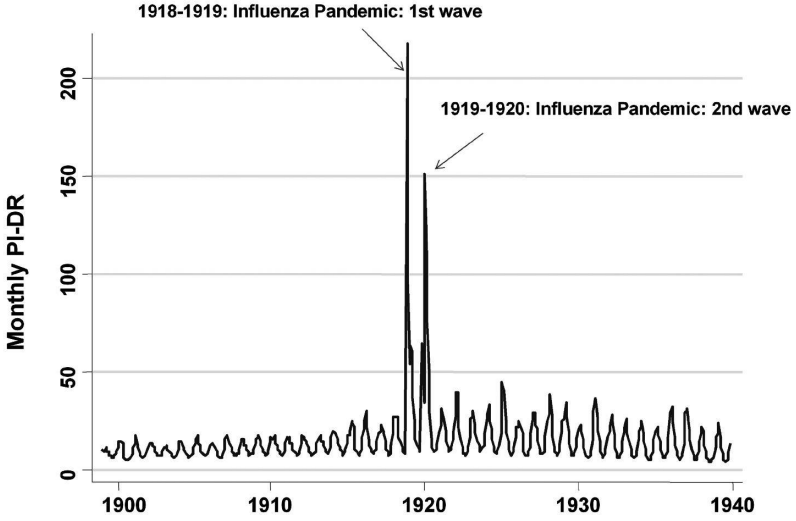

Fig. 1E. An epidemic curve of monthly PI-DRs around the time of influenza pandemics from 1899 to 1940.

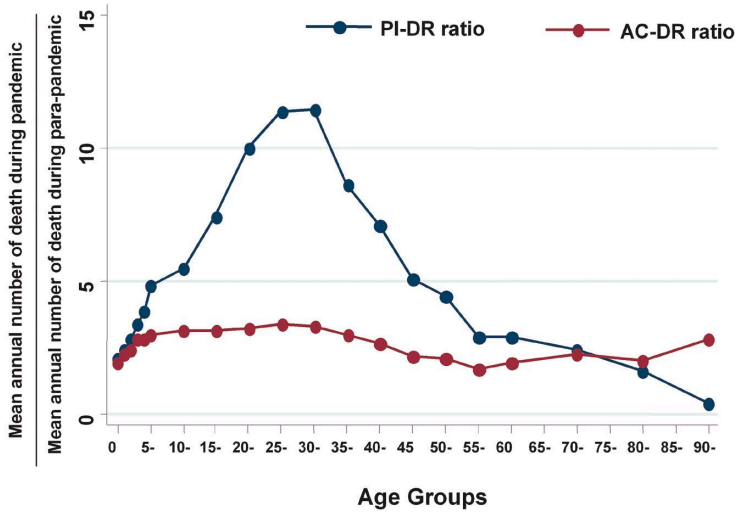

Fig. 2. Ratios of annual number of death during pandemic flu period (1918–1920)/parapandemic periods (1915–1917, 1921, 1922), stratified by age group.

tions was large but gradually decreased over time.

Stratifications by age group and ratios of the mean annual number of deaths during pandemic periods (1918, 1919, 1920) and parapandemic periods (1915, 1916, 1917, 1921, 1922) are shown in Fig. 2. The PI-DR increased more than 10 times during the pandemic period in the 25 to 30-year age group and more than 5 times during the pandemic period in all age groups between 10 and 45 years. These increases were not obvious in the AC-DR.

EDRs during the Spanish flu pandemic

Next, monthly EDRs during the pandemic period from January 1918 through December 1920 were calculated for Japan and for each prefecture. The excess deaths due to all causes and excess deaths due to pneumonia or influenza during the 3 years numbered 577,115 (1.03% of the population in 1917) and 444,305

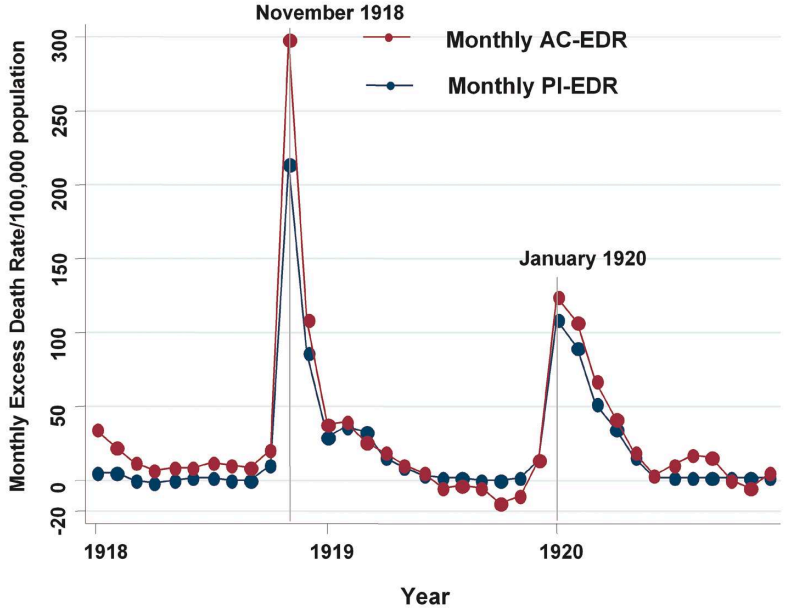

Fig. 3. Monthly AC-EDR and PI-EDR/100,000 persons during the Spanish flu pandemic.

(0.79% of the population in 1917), respectively. Monthly changes in the AC-EDR and PI-EDR are shown in Fig. 3. Both the AC-EDR and PI-EDR showed similar epidemic curves, with 2 peaks. The first peak, in November 1918, was steeper and higher than the second peak in January 1920, as indicated by statistical differences in maximum growth rate ($P < 0.0001$) and the peak PI-EDR/month ($P < 0.0001$) using data from 47 prefectures. The AC-EDR and PI-EDR for the 18 months of the first half of the 3-year Spanish flu pandemic period, from January 1918 to June 1919 including the first peak, contained 64% and 54% of all excess deaths over the 3 years; these values were significantly higher than those during the 18 months of the second half, from July 1919 to December 1920 ($P < 0.0001$).

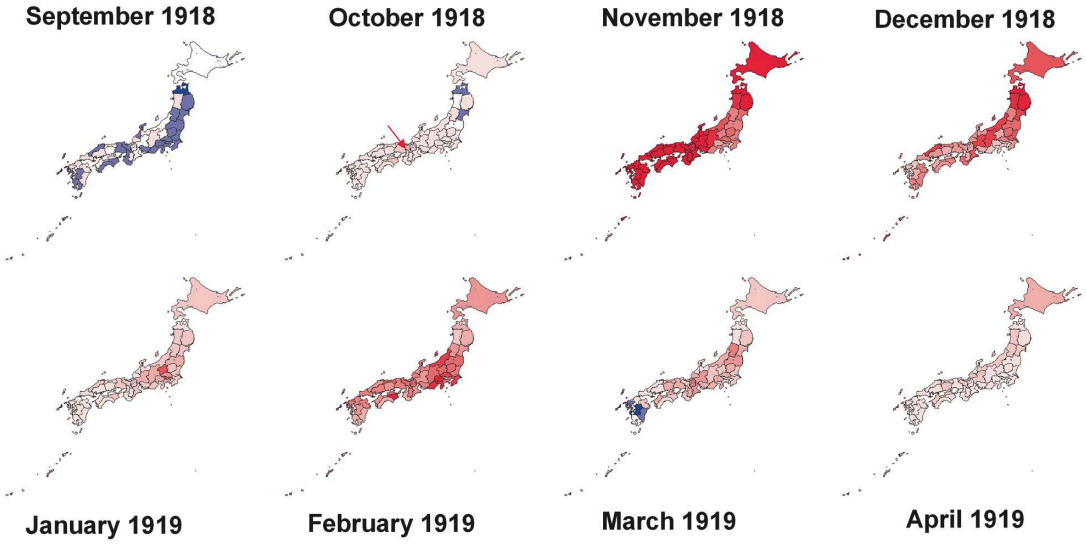

Fig. 4A. Geographical spread of the change in the PI-EDR during the first wave of the Spanish flu pandemic from September 1918 to April 1919. Blue indicates negative EDR, white indicates 0 to 10 PI-EDR, and colors from pink to red with gradation are stratified by levels of PI-EDR. The darkest red represents a PI-EDR of more than 200/month. The arrow indicates the Osaka/Hyogo district, where the epidemic appeared to have started.

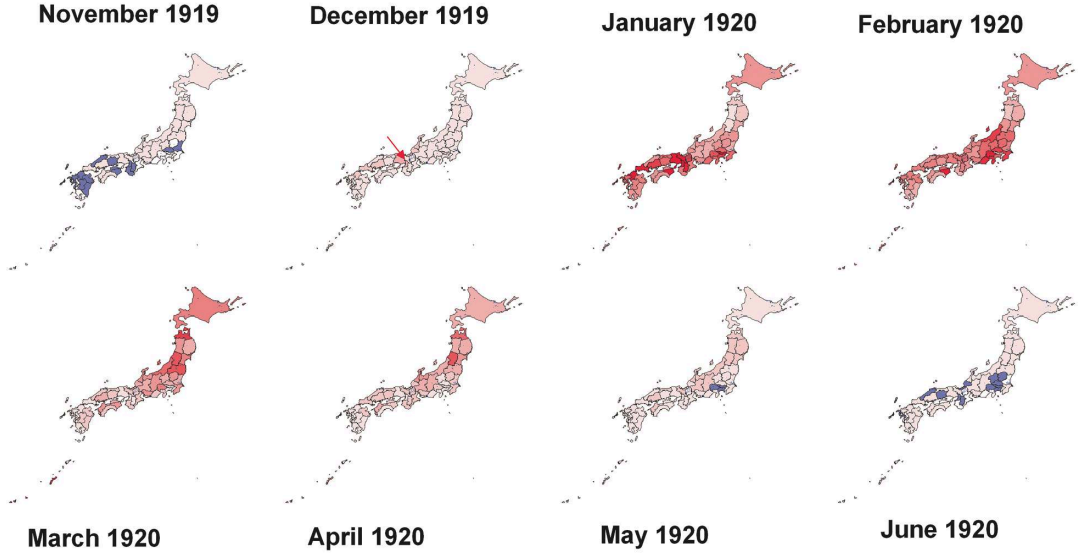

Fig. 4B. Geographical spread of the change in the PI-EDR during the second wave of the Spanish flu pandemic from November 1919 to June 1920.

Next, we used maps to determine the pattern of spread of lethal influenza through time and space around the first peak, from September 1918 to April 1919 (Fig. 4A), and around the second peak, from November 1919 to June 1920 (Fig. 4B). The PI-EDR started to increase in Osaka, Hyogo, and adjacent prefectures in October 1918 and then gradually increased all over Japan during the next few months (Fig. 4A). Although the PI-EDR decreased in January 1919, it increased again in February 1919. For the second peak, the PI-EDR again started to increase in Osaka and Hyogo in December 1919 and gradually increased all over Japan during the next few months, although the increase was slower and the pattern

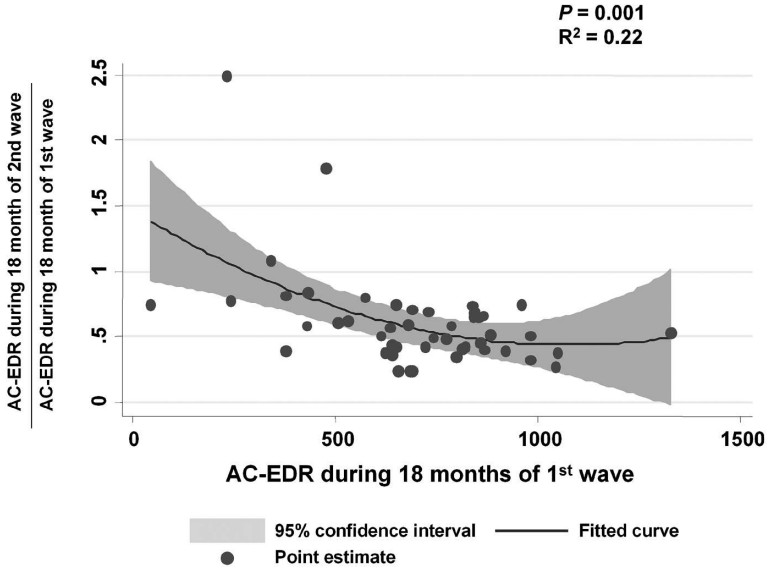

Fig. 5A. Association between AC-EDR during the first 18 months of the Spanish flu pandemic (the first half) and AC-EDR during the second 18 months of the Spanish flu pandemic (the second half)/AC-EDR during the first half.

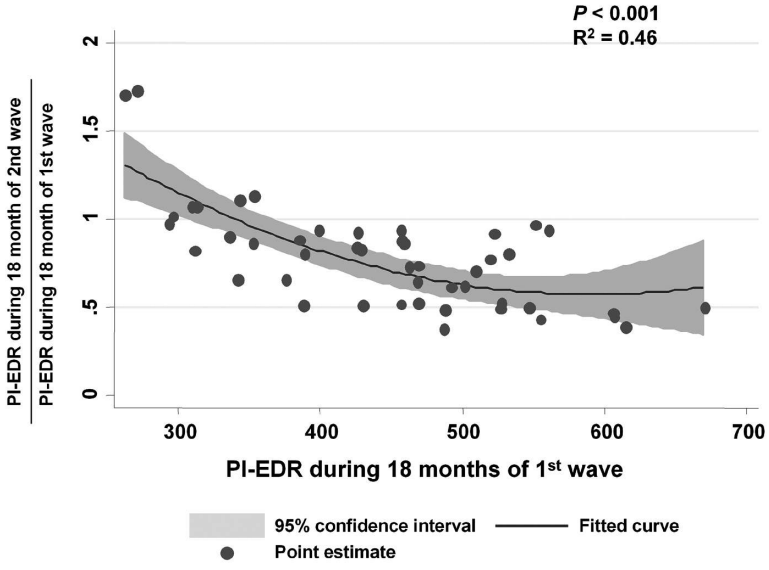

Fig. 5B. Association between PI-EDR during first 18 months of the Spanish flu pandemic (the first half) and AC-EDR during the second 18 months of the Spanish flu pandemic (the second half)/AC-EDR during the first half.

differed from that of the first peak (Fig. 4B).

To determine whether prefectures with a higher EDR during the first half of the pandemic had a reduced EDR during the second half, or, in contrast, if those with a lower EDR in the first half had an increased EDR in the second half, we created a new parameter—the natural logarithm of the ratio of the EDR during the 18 months of the second half/the EDR during the 18 months of the first half—and compared it with the EDR during the first half. There were statistically significant inverse relationships both in the AC-EDR (Fig. 5A) and the PI-ECR (Fig. 5B), indicating that when the EDR in the first half was high, the EDR in the second half was reduced, and vice versa.

Factors affecting variability of the EDR in the 47 prefectures

The AC-EDR in Kagawa (2031) was 13.6 times as high as that in Tokyo (149), and the PI-EDR in Tokushima (1089) was 1.9 times as high as that in Kumamoto (566). We attempted to clarify which factors affected the variability of the EDR in the 47 prefectures by constructing multiple regression models with backward elimination using a cutoff point of $P=0.005$ (Table 1). A higher illegitimate/legitimate birth ratio and a lower population density in 1917, 1 year before the Spanish flu pandemic started, were associated with higher a AC-EDR; 32% of the variability in the AC-EDR observed in the 47 prefectures was explained by only these 2 factors. Similarly, a higher illegitimate/legitimate birth ratio and a higher death rate of 1-year-olds in 1917 were associated with a higher PI-EDR; 32% of the variability in the PI-EDR was explained by these 2 factors. The major causes of death for 1-year-olds in 1917, listed in the vital statistics, were diarrhea (29% of total deaths), pneumonia (23%), meningitis (11%), and measles (4%).

Discussion

As seen in long-term trends for death rates in Japan, 2 conspicuous peaks occurred from 1918 to 1920 (the Spanish flu pandemic period). The amplitude of annual oscillations was marked around and after 1918. In contrast, the amplitude of annual oscillations was reduced after the 1950s, and no spikes in the death rate occurred around 1957 (the Asian flu) or 1968 (the Hong Kong flu). Murray et al. have analyzed vital registry data from 26 countries during and around the Spanish flu pandemic and has concluded that per-capita income was the most powerful predictor of death rate[10]. Japan underwent rapid economic growth and improved access to healthcare after the 1960s, which may explain the reduction in the amplitude of annual oscillations in the I-DR and PI-DR and the minimized peaks during the Asian flu and Hong Kong flu pandemics. However, the mortality rate is affected by the incidence and prognosis of the disease. Because there were no exact data on the incidence of influenza in each prefecture during the study period, we cannot conclude that the prognosis of influenza may be improved by the times. Neverthe-

Table 1. Multiple regression model to explain the variability of excess death rates observed within 47 prefectures: backward elimination with a cutoff point of $P=0.2$.

Dependent variable	R^2	Predictor variables	β	Standard error	P value	t
AC-EDR	0.47	Illegitimate/legitimate birth ratio	49.81	11.55	<0.001	4.31
		Population density in 1917	−0.503	0.132	<0.001	−3.82
		Infant death rate in 1917	−132.1	46.43	0.007	−2.85
		Total death rate in 1917	101.44	30.04	0.002	3.38
PI-EDR	0.45	Illegitimate/legitimate birth ratio	19.55	4.392	<0.001	4.45
		Death rate of 1-year-olds/1,000 population	258.25	84.20	0.004	3.07
		Death rate of persons younger than 5 years in 1917	−50.04	21.99	0.028	−2.28
		Total death rate in 1917	38.47	12.59	0.004	3.05

AC-EDR, all-cause excess death rate; PI-EDR, pneumonia/influenza excess death rate

less, even if we could obtain incidence data, the diagnostic criteria must differ considerably by era. Moreover, access to medicine might differ by era, and many patients did not consult physicians during febrile illnesses during the Spanish flu pandemics.

The question of why so many people, especially young and healthy people, died from the Spanish flu remains unanswered[13]. In the present study, we created a simple variable : the ratio of the annual PI-DRs during the pandemic and parapandemic periods stratified by age. We found that ratios were most increased in the 25 to 30-year age group, as has been observed in other counties[1]. Conversely, the ratios in the older age groups, in which death rates are usually high during influenza seasons, were low. In the summary report published in 1922[16], Japan, as well as many other countries, experienced an influenza pandemic in 1889, but after that, no major influenza epidemics occurred until 1918. Indeed, in this longitudinal study no prominent epidemics were recognized from 1899 to 1917. Adults aged 25 to 30 years were born between 1888 and 1893, which suggests that this generation had not been exposed to any influenza epidemic or pandemic until 1918, when the Spanish flu pandemic occurred. In contrast, the older age groups may have been protected by immunity gained in 1889 and earlier, as suggested by Morens and Fauci[13].

In the 1922 summary report[16], 23,804,673 persons, 42% of the population of Japan, were infected with influenza, and 388,727 (0.69%) of them died of influenza from August 1918 to July 1921, suggesting an influenza mortality rate of 1.63%. In contrast, we used data from vital statistics and concluded that during the 3 years of the Spanish flu pandemic there were 577,115 excess deaths due to all causes (1.03% of the population in 1917) and 444,305 excess deaths due to pneumonia/influenza (0.79% of the national population in 1917). We suspect that the differences in numbers were due to the 1922 summary report[16] not using the concept of EDR and, thus, underestimating death rates. Similarly, the cause of death was not always recorded accurately, and the PI-EDR might underestimate the rate of deaths due to the Spanish flu.

In the present study, we found that prefectures with a higher EDR during the first half of the pandemic had a lower EDR during the second half, and vice versa. This finding suggests that persons who survived the first half of the pandemic developed immunity against the Spanish flu and were protected during the second half and that people who did not contract the flu during the first half of the epidemic did not develop immunity and contracted the flu during the second half. Thus, immunity against influenza may play a key role in reducing death rates during a pandemic.

In Japan's 47 prefectures, we observed differences of 13.6 times in the AC-EDR and 1.9 times in the PI-EDR. During the 1918 to 1920 pandemic, diagnostic accuracy at death could differ greatly among prefectures and might cause severe bias in the PI-EDR. A higher illegitimate/legitimate birth ratio and total death ratio in 1917 were associated with a higher AC-EDR and PI-EDR, a finding that is consistent with the report of Bootsma and Ferguson showing that variability in the EDR among 23 United States cities in 1918 was significantly correlated with the 1917 per-capita mortality[11]. We did note a strong correlation with the mortality rate of 1-year-olds in the PI-EDR. The main causes of death in 1-year-olds in 1917 were diarrhea, pneumonia, meningitis, and measles ; with modern medicine, these conditions can either be prevented or successfully treated with early intervention. Population density in 1917 was negatively correlated with the AC-EDR but not with the PI-EDR. As mentioned above, PI-EDRs can include significant bias.

Unexpectedly, the present study found that areas with a higher population density had a lower AC-EDR, unlike a previous study that showed no correlation between population size or density and the EDR[8]. One possible reason for this finding is that the "flu" in its mild form was prevalent during the summer in Tokyo, Kanagawa, and other cities with large populations where people developed immunity before contracting the Spanish flu. Such immunity would lead to a lower AC-EDR in these areas. Another explanation is that people in large cities would have better access to healthcare and higher quality medication, nutrition, and economic status. In the present study, higher illegitimate/legitimate birth ratios were

related to higher AC-EDRs and PI-EDRs; to our knowledge, this is the first report to examine representative socioeconomic factors. These 3 factors—the higher illegitimate/legitimate birth ratio, the lower population density in 1917, and the higher death rates of 1-year-olds in 1917—may suggest that the quality of community health and the regional socioeconomic status during peacetime may be key factors, at least in part, in controlling an influenza pandemic.

Although there are at least several major limitations of the present study, 2 of them can be explained as follows. 1) Due to the nature of an ecological study involving a broad geographic area, we cannot determine the precise mechanisms that lead to the increased EDRs. In particular, we did not have individual data, such as comorbidity of chronic diseases, pregnancy, and body mass index, that were seen in the influenza pandemic of 2009. 2) Moreover, we used both the AC-EDR and PI-EDR in this study. The PI-EDR may be more biased than the AC-EDR because of the inaccuracy in the diagnoses of pneumonia and influenza. However, in the case of the AC-EDR, the deaths may include mass casualties due to disasters or changes in the rates of other infectious diseases, including smallpox and polio.

Contributions

M Urashima conceived the idea, collected, and led the analysis.

T Shimada assisted with interpretation and the drafting of the manuscript.

All authors read and approved the final version of the manuscript.

Conflict of Interest Statement

We declare that we have no conflict of interest.

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