Original Article

Influence of Average Income on Epidemics of Seasonal Influenza

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SUMMARY: Understanding the local factors influencing the transmission of communicable diseases is important to minimize social damage. The aim of this study was to investigate local factors influencing seasonal influenza epidemics in Aomori prefecture consisting of 6 regions, i.e., Seihoku, Chunan, and Tosei on the west side, and Sanpachi, Kamikita, and Shimokita on the east side. Four indices (epidemic onset, duration, scale, and steepness of epidemic curves) were defined, and their correlations with regional characteristics and meteorological factors were investigated. Data for influenza seasons from 2006–2007 to 2014–2015 were collected. The 2009–2010 season was excluded because of the pandemic of A (H1N1)pdm09. Average income was strongly correlated with epidemic onset, duration, and scale. The ratio of children aged ≤5 years to the total population was strongly correlated with epidemic duration and scale. Low temperature in January showed moderate correlation with epidemic duration and scale. Cluster analysis showed that 2 isolated regions, Seihoku and Chunan, belonged to the same cluster in the 4 indices of epidemic curves, and other 2 relatively urbanized regions formed another cluster in 3 of the 4 indices. This study highlights important local factors that influence seasonal influenza epidemics and may help in implementation of preventive measures.

INTRODUCTION

Seasonal influenza is a common infectious disease that peaks in winter in most parts of Japan. A sentinel surveillance system for seasonal influenza, consisting of 3,000 pediatric and 2,000 internal medicine sites, is currently operating in Japan (1). The Aomori prefecture has approximately 1.3 million people and an area of 9,644.55 square meters. It is located in the northernmost tip of the main island of Japan (Fig. 1). The Aomori prefectural government divided the Tsugaru area into the Tosei, Chunan, and Seihoku regions, and the Nambu area was divided into the Sanpachi, Kamikita, and Shimokita regions. The geographical, socio-cultural and meteorological conditions differ within Aomori prefecture. It is important to understand the characteristics of seasonal influenza epidemic patterns in local areas in order to implement better preventive measures. Therefore, in this study, we aimed to investigate the factors influencing the differences in the patterns of seasonal influenza epidemics among the various regions of Aomori prefecture.

MATERIALS AND METHODS

Data source and extraction: In Japan, influenza-like illness has been monitored under the national surveillance system since 1987. The National Institute of Infectious Diseases has been accumulating data from approximately 5,000 nationwide sentinel medical facilities on a weekly basis. The epidemic threshold for influenza is defined as 1.0 case per sentinel per week based on the accumulated data. Epidemiological data on seasonal infectious Diseases has been accumulating data from approximately 5,000 nationwide sentinel medical facilities on a weekly basis. The epidemic threshold for influenza is defined as 1.0 case per sentinel per week based on the accumulated data. Epidemiological data on seasonal...
influenza epidemics were collected for the 2006–2007 to the 2014–2015 influenza seasons using data from the sentinel surveillance system in Aomori prefecture. The local governmental organizations in Aomori, as a division of national surveillance system, in each of the 6 regions in Aomori compile cases of influenza from the 65 local sentinel sites. All data since 2007 are available to the public on the Aomori prefectural government website. Seasonal influenza epidemics started in late January in the 2006–2007 season; therefore, data collected from the 2006–2007 to the 2014–2015 seasons were obtained. Data of the 2009–2010 season, in which the A (H1N1)pdm09 strain prevailed, were excluded from this study. Four indices were defined: epidemic onset, duration, scale, and the steepness of the epidemic curve. The onset of an influenza epidemic was defined as the week when the number of cases per sentinel site exceeded 1.0, and the end of the epidemic was defined as the week when that number dropped below 1.0. For the comparison of the onset and the end of epidemics, the week including January 4 was defined as the “0” point. If the epidemic began 1 week before (or after) the “0” point, the time of onset was counted as −1 (or 1). The epidemic scale is the sum of the reported cases from the sentinels during the epidemic (patients/season). The steepness of the epidemic curve was calculated by dividing the largest number of cases in the season by the epidemic duration (Fig. 2). Differences in the patterns of seasonal influenza epidemics in Aomori were analyzed using the following 3 steps.

Cluster analyses: The epidemic patterns were classified by cluster analysis of the 4 indices. Data of each index were collected from the 8 seasons (the 2006–2007 to the 2014–2015 seasons excluding the 2009–2010 season). Hence, each region had 8 data sets. Common characteristics of the regions with similar epidemic patterns were examined.

Correlation coefficient (CC) of the regional characteristics: We investigated correlations among the 4 indices and regional characteristics by calculating the Pearson product-moment correlation coefficient. Data were obtained from the Aomori prefectural government website. Regional characteristics included total population, the number of doctors, population density, the number of households and average income. During the study period (from 2006 to 2014, excluding 2009), data on the total population and population density were available until 2014 (8 fiscal years); on the number of doctors, until 2013 (7 fiscal years); on the average income, until 2012 (6 fiscal years); and on the household population, until 2010 (4 fiscal years). The average values of these regional characteristics during the available period were calculated for each of the 6 regions as well as the 4 indices. Subsequently, the correlations between the average value of the 4 indices and the regional characteristics, both representing the 6 regions, were investigated. The correlation was considered as weak, moderate, strong, and very strong for absolute CC values of 0.20–0.39, 0.40–0.59, 0.60–0.79 and 0.80–1.00, respectively.

CC of meteorological factors: Seasonal influenza endemic patterns vary every year. We investigated correlations of the above-mentioned 4 indices of influenza epidemic curves every year and monthly meteorological data from November to March by calculating the Pearson product-moment correlation coefficient. Meteorological data were obtained from the Japan Meteorological Agency website and included the seasonal average temperature, maximum temperature, minimum temperature, and difference between the maximum and minimum temperatures, daily maximum temperature, daily minimum temperature, daily temperature difference, snow accumulation, and absolute and relative humidity. The data on both seasonal influenza epidemics and the meteorological records on temperature and snow accumulation were available in every region during the study. Each of the 6 regions has 8 data sets; hence, the total number of data sets was 48 in the investigation for the correlations between the 2 meteorological factors (atmospheric temperature and snow accumulation) and the 4 indices. The data on humidity were available in 3 regions for 8 seasons, and the total number of data sets was 24.

Statistical analysis: The statistical analysis was carried out using EZR (2) and Mulcel (OMS Publishing, Saitama, Japan), an add-in software for Excel (Microsoft, Redmond, WA, USA). Significance was set at $p < 0.05$.

Ethics statement: The ethics committee of Hirosaki University Graduate School of Medicine deemed this study as an analysis of de-identified and publicly available data, which did not need to be reviewed.

RESULTS

Average of the indices: The average for each index was calculated (Table 1). In the Kamikita region, which lies east of the Hakkoda Mountains, seasonal influenza epidemics affect a large number of people and have an early onset. In the Chunan and Seihoku regions, in the western part of the prefecture, epidemics were smaller in scale.

Classification of epidemic curves in the 6 regions of Aomori: Cluster analyses showed similarities in the epidemics (Fig. 3). The Tosei and Sanpachi regions, which are the urbanized regions of Aomori prefecture, were in the same cluster with respect to epidemic onset, scale, and steepness of the epidemic curve. In addition, the Chunan and Seihoku regions, which lie in the west of
Aomori prefecture, were in a cluster with respect to epidemic onset, scale, and steepness of the epidemic curve.

**Correlation with regional characteristics:** We investigated correlations of each of the 4 indices with regional characteristics (Table 2). Average income showed a very strong negative correlation with epidemic onset and a very strong positive correlation with epidemic duration and scale. The percentage of children aged 0–5 years, and in particular, the rate of children aged 3–5 years who started attending preschool, showed a very strong positive correlation with epidemic duration and scale. The percentage of primary school children also showed a very strong correlation with epidemic duration.

**Correlation with meteorological factors:** We investigated correlations of the 4 indices every year with meteorological factors. Factors for temperature included monthly average temperature, maximum temperature, minimum temperature, difference between maximum and minimum temperature, daily maximum temperature, daily minimum temperature, and daily temperature difference for November to March. Factors that were temperature were correlated with 4 indices were extracted and are presented in Table 3.
Epidemic onset had a weak positive correlation with average temperature in November, daily minimum temperature in November, and minimum temperature in December, and a weak negative correlation with temperature difference in December. The higher the temperature in late autumn, the later the epidemic tended to begin. Furthermore, the larger the difference between the minimum and the maximum temperature in December, the earlier the epidemic tended to begin.

Epidemic duration had a weak-to-moderate negative correlation with the minimum temperatures and the minimum temperature difference in December. The higher the temperature difference in December, the earlier the epidemic tended to begin. Furthermore, the larger the difference between the minimum and the maximum temperature in December, the earlier the epidemic tended to begin.

A variety of factors have been proposed to explain the seasonality of influenza, including low temperature, low humidity, solar radiation, daylight hours, crowding, population movement, age distribution, melatonin level, vitamin D level, and selenium level (1,3–5). Most countries have 1 annual influenza epidemic. In contrast, about half of the tropical countries have 2 or 3 influenza endemics per year (6). The epidemic pattern of seasonal influenza was thought to differ from place to place in Aomori prefecture; however, to our knowledge, no epidemiological study has been performed previously regarding this issue. In this study, several local meteorological, social, and demographic factors were found to be correlated with the epidemic patterns of seasonal influenza.

The rate of children aged 0–5 years had a strong correlation with epidemic duration, scale, and steepness of epidemic curves. Children develop anti-influenza virus CD8 T-cell memory comparable with that of adults by the age of 15 years (3). In this study, we found an increased risk of influenza transmission through preschool contact as compared with school and adult contact. Children are vulnerable to influenza infection (7); in particular, children aged 3–5 years who start preschool do not have adequate immunity, and are thus more likely to become infected. Therefore, they are thought to play an important role in seasonal influenza epidemics. In a study including households with primary or junior high school-aged children, influenza transmission was most commonly observed between primary school children and parents, followed by transmission from primary school children to siblings (8). For the control of seasonal influenza, vaccination of
80% of the children has been reported to be as effective as vaccination of 80% of the entire population (9). However, it was reported that vaccination did not reduce the frequency of infection in children aged <13 years (10). As such, comprehensive prevention of infection of preschool children is important. Unexpectedly, among the various factors investigated in this study, the average income showed a very strong correlation with 4 indices. The average income includes employee compensation, property income, and entrepreneurial income, reflecting economic activity. Movement of people is more closely correlated with regional spread of influenza than geographical distance between regions (11,12). Regions with high economic activity are thought to comprise more people who travel; therefore, seasonal influenza epidemics in these areas may start early and expand over a larger area, as was observed in Seihoku and Sanpachi regions. The Seihoku and Sanpachi regions include Aomori city with a population of 240,000, respectively, and are relatively urbanized and Sanpachi regions include Aomori city with a population of 300,000 and Hachinohe city with a population of 134,000, respectively, and are relatively urbanized. Furthermore, Aomori city and Hachinohe city are directly connected with the city and Hachinohe city are directly connected with the Sanpachi regions. The Seihoku and Sanpachi regions are thought to comprise more people who travel; therefore, seasonal influenza epidemics in these areas may start early and expand over a larger area, as was observed in Seihoku and Sanpachi regions. The Seihoku and Sanpachi regions include Aomori city with a population of 240,000, respectively, and are relatively urbanized. Furthermore, Aomori city and Hachinohe city are directly connected with Shinkansen by a 25-min route and are linked to Tokyo.

### Table 3. Correlation between 4 indices and temperature

| Index                | Month  | Temperature         | CC       | p    |
|----------------------|--------|---------------------|----------|------|
| Epidemic onset       | November | average temperature | 0.359    | 0.012|      |
|                      |        | daily minimum      | 0.359    | 0.012|      |
|                      | December | temperature         | 0.309    | 0.033|      |
|                      |        | difference          | −0.397   | 0.005|      |
| Epidemic duration    | December | minimum temperature | −0.508   | 0.0002|    |
|                      |        | difference          | 0.523    | 0.0001|    |
|                      |        | daily temperature   | 0.526    | 0.0001|    |
|                      | January | average temperature | −0.348   | 0.015|      |
|                      |        | minimum temperature | −0.479   | 0.0006|    |
|                      |        | temperature         | 0.435    | 0.002|      |
|                      |        | difference          | −0.504   | 0.0003|    |
|                      | February | daily temperature  | 0.566    | 0.00003|    |
|                      |        | difference          |         |      |      |
| Epidemic scale       | December | minimum temperature | −0.329   | 0.023|      |
|                      |        | daily temperature   | −0.326   | 0.024|      |
|                      |        | difference          | 0.389    | 0.006|      |
|                      | January | minimum temperature | −0.526   | 0.0001|    |
|                      |        | temperature         | 0.606    | 0.00005|    |
|                      |        | difference          | −0.348   | 0.015|      |
|                      |        | daily temperature   | 0.443    | 0.002|      |
|                      |        | difference          |         |      |      |
| Steepness of epidemic curves | November | daily temperature  | 0.327    | 0.023|      |
|                      |        | difference          |         |      |      |
|                      | December | maximum temperature | −0.437   | 0.002|      |

### Table 4. Correlation between 4 indices and humidity

| Index                      | Factor              | CC       | p    |
|----------------------------|---------------------|----------|------|
| Epidemic onset             | November absolute humidity | 0.574    | 0.003|      |
|                           | March absolute humidity | −0.506   | 0.012|      |
| Epidemic duration          | March absolute humidity | −0.451   | 0.027|      |
| Epidemic scale             | March relative humidity | 0.425    | 0.038|      |
|                           | March minimum relative humidity | 0.485 | 0.017|      |
| Steepness of epidemic curves | March relative humidity | 0.508    | 0.011|      |

### Table 5. Multiple linear regression analysis for the impact of social and meteorological factors on epidemic curves

#### A. Social factors

| Epidemic curve index | Regression equation | p value |
|----------------------|---------------------|---------|
| Onset (wk)           | −0.00137 (avg. income) + 2.67 | 0.021   |
| Duration (wk)        | 0.0057 (avg. income) + 6.77 | 0.00024 |
| Scale (patients)     | 0.20 (avg. income) − 222.6 | 0.015   |
| Steepness index      | 2.21 (3–5-year-old children [%]) − 2.97 | 0.060   |

#### B. Temperature

| Epidemic curve index | Regression equation | p value |
|----------------------|---------------------|---------|
| Onset (wk)           | 1.33 (Nov. avg. temp.) − 0.34 (Dec. temp. diff.) − 3.25 | 0.0026  |
| Duration (wk)        | −0.52 (Mar. daily min. temp.) + 0.42 (Mar. temp. diff.) + 0.4 (Dec. temp. diff.) + 0.38 (Jan. daily temp. diff.) − 0.85 | 0.00000173 |
| Scale (patients)     | 13.3 (Jan. temp. diff.) − 11.4 (Feb. daily min. temp.) − 28.9 | 0.000118 |
| Steepness index      | 0.34 (Nov. daily temp. diff.) − 0.22 (Dec. max. temp.) + 1.80 | 0.000174 |

#### C. Humidity

| Epidemic curve index | Regression equation | p value |
|----------------------|---------------------|---------|
| Onset (wk)           | 5.0 (Nov. absolute humid.) − 2.97 (Mar. absolute humid.) − 17.6 | 0.0011  |
| Duration (wk)        | −4.1 (Mar. absolute humid.) + 37.1 | 0.027   |
| Scale (patients × 10^3) | 8.2 (Mar. relative humid.) + 7.8 (Mar. min. relative humid.) − 521.2 | 0.019   |
| Steepness index      | 0.14 (Mar. relative humid.) − 7.5 | 0.022   |
Although the Chunan and Seihoku regions were once the main regions of the Tsugaru domain, they are now relatively isolated regions in Aomori prefecture. The average income has a very strong positive correlation with the average percentage of children aged 0–5 years (CC = 0.934, \( p = 0.0063 \)), as more children may be born in regions with high economic activity. However, no correlation was observed between snow accumulation and the 4 indices analyzed in this study. Heavy snowfall during winter in the Aomori prefecture poses difficulty. Snow accumulation may prevent people from going outdoors and therefore could contain the spread of seasonal influenza. However, regardless of the snow, children go to their nursery, preschool, or elementary school just as adults go to their workplace.

In this study, the minimum temperature and temperature difference correlated with epidemic onset, duration, and scale. Specifically, minimum temperature and temperature difference in December were correlated with epidemic onset (CC = 0.309 and \(-0.397\), respectively), which may be because the seasonal influenza epidemics start in December in many cases. Epidemic duration was correlated with the daily minimum temperature (CC = \(-0.504\)) and temperature difference (CC = 0.435) in January, which is the coldest month of the year. The epidemic scale was correlated with the minimum temperature (CC = \(-0.526\)) and temperature difference (CC = 0.606) in January. Low temperature causes cold stress, which depresses immune responses (13,14). Furthermore, cold stress due to temperatures \(<0\)°C causes death from respiratory disease in humans (15,16). The atmospheric temperature difference also affects humans. Medium-term (7–10 days) and long-term (\(\geq 3\) weeks) atmospheric temperature changes were associated with highly significant changes in rates of death from pneumonia (17,18). Constantly low temperature and a large temperature difference may lead to a longer duration of epidemics. The lowest temperature and largest temperature difference in a month may cause epidemics on a large scale. Additionally, a high maximum temperature in December could cause a gentle epidemic curve slope.

In this study, the humidity in March may be a factor that influences seasonal influenza epidemics. Relative humidity is the amount of water vapor in the air, expressed as a percentage of the maximum amount that the air could hold at a given temperature, whereas absolute humidity is the mass of water vapor present in a unit volume of moist air. Therefore, if the temperature of air increases, the relative humidity reduces without changing the amount of water vapor or absolute humidity. The influenza virus is maximally stable at low relative humidity (19). Low absolute humidity is associated with influenza outbreaks in human populations (20,21). Absolute humidity affects both influenza virus transmission and influenza virus survival to a larger extent than relative humidity (22). The onset of winter-time influenza is associated with low absolute humidity in the United States (19). These reported observations are consistent with our results that showed the epidemic onset had a moderate correlation with absolute humidity in November, and epidemic duration had a moderate negative correlation with absolute humidity in March. The higher the humidity, the later the epidemic may begin and the earlier it may end. The result that warm and humid climate in November delays the onset of epidemics and warm and humid climate in March shortens the duration was plausible. However, it was unclear why the absolute humidity in March had a negative correlation with the epidemic onset, and relative humidity in March affected the epidemic scale and steepness index.

Taken together, these results related to the regional characteristics may explain the results of cluster analysis. Seihoku and Chunan regions are both relatively isolated regions that share the same cultural and geographical background, formed a cluster in the 4 indices for epidemic curves, and Tosei and Sanpachi regions, which are relatively urbanized area of Aomori prefecture connected with Shinkansen, formed another cluster in 3 of the 4 indices.

This study has some study limitations. This study was a local, not global, study conducted using local meteorological and demographic data of Aomori prefecture, Japan. And this study did not include analysis of several important factors (e.g., vaccination rate, educational activities for infection control, consumption rate of hand disinfectant products, and traffic density) that may affect the epidemic curve of seasonal influenza, because we could not obtain sufficient data representing these factors for each region of Aomori prefecture.

In conclusion, the results of this study indicate the importance of local and social factors such as climate, population composition, income, and urbanization, for seasonal influenza epidemics. It would be beneficial to determine the regional differences of these factors in order to develop effective preventive countermeasures for seasonal influenza epidemics and other communicable diseases.

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Conflicts of interest None to declare.

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