Original Article

Geographic Spread of Influenza under the Influence of Community Population Size, Which Differed from That of Measles and Rubella

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SUMMARY: The influenza season is defined as the period from week 36 of the year to week 20 of the subsequent year in this report. The population size of prefectures (x) and number of patients per prefecture (y) were initially uncorrelated, but a correlation developed as the season advanced. The correlation with correlation coefficient > 0.7 emerged increasingly earlier over time; it developed in week 5 of the subsequent year in 2001/2002, but in week 47 of the same year in 2014/2015. Once x and y were correlated, plots of y on the vertical axis against x on the horizontal axis resulted in a straight line, \( y = Cx^s \), where \( s \) was the slope of the plot and \( C \) was a constant. The slope was high (\( s > 1 \)) initially, but decreased (\( s < 1 \)) later, indicating that influenza first spread to populated prefectures and then nationwide, involving less populated prefectures. This spread pattern was the same for the seasonal influenza and AH1pdm2009, although the progression of the latter was much faster. For measles and rubella epidemics, the number of patients per prefecture was proportional to the square of the population size from the start to the end of the season.

INTRODUCTION

This paper examines the effect of community population size on the spread of influenza over time between 2001 and 2015 in Japan, and compared it with its effect on measles and rubella. As population size and population density were highly correlated in Japan (correlation coefficient, CC: 0.89) (1), the observation made for population density was true for population size.

MATERIALS AND METHODS

Seasonal influenza is a sentinel-based reportable infection. The sentinel sites were selected from medical facilities in a health center’s jurisdiction; the number of sentinel points per health center was 1 for a population of <30,000, 2 for a population of 30,000–75,000, and 3 for a population >75,000. Currently, there are a total of about 5,000 sentinels in Japan (2).

“Influenza weekly morbidity data are available from the Table (SENTINEL-REPORTING DISEASES <WEEKLY> Number of cases per sentinel by sex, prefecture, and week) and those of measles and rubella from the Table (NOTIFIABLE DISEASES Number of cases by sex, prefecture and week). Those ‘Table’ data can be downloaded from the NIID’s homepage regarding National Epidemiological Surveillance of Infectious Diseases (NESID) (https://www.niid.go.jp/niid/ja/survei/2270-idwr/nenpou/6982-syulist2015.html).”

The demographic data were obtained from the vital statistics of the population based on basic resident registry (https://www.e-stat.go.jp/SG1/statat/GL08020102.do?_toGL08020102__tclassID=00001028704&cycleCode=7).

RESULTS

Influenza: The influenza season generally begins in autumn and ends in spring in Japan. The Ministry of Health, Labour, and Welfare (MHLW) released the “weekly announcement on influenza” starting from week 36 of the year (September) until week 20 of the next year (May) (http://www.mhlw.go.jp/stf/seisakunitsuite/bunya/kenkou_iroyou/kenkou/kekkaku-kansenshou01/houdou.html). This report used the same calendar; consequently, the years of the influenza seasons were expressed as 2013/2014, 2014/2015, etc., as shown in Fig. 1A-1. Fig. 2A-1 shows a plot of the cumulative number of influenza patients per prefecture (y-axis) against the prefecture population (×1,000) (x-axis) at different periods in the influenza season. Table 1A summarizes CCs between the cumulative number of patients and the population size (upper part) and slopes of the plots derived from the plots in Fig. 2A-1 (lower part). In the initial phase, there was no correlation between the population size and the number of patients. A correlation with CC > 0.7 emerged later, i.e., in week 17 of the next year in 2001/2002, in week 5 of the next year from 2004/2005 to 2010/2011, in week 52 of the same year in 2013/2014, and in week 47 of the same year in 2014/15. Thus, the initial phase with random distribution of the patients (CC < 0.7) shortened over the years. Once the correlation between the population size and number of patients (CC > 0.7) was established, the plots first resulted in a steep (\( s > 1 \)) approximation line and then in a flatter (\( s \leq 1 \)) line (Fig. 1A-1). For example, in 2014/2015, it was approximately 1.2 in weeks 47 and 52, but was approximately 0.8 in weeks 5 and 17 of the next year; a similar tendency was observed in other years (lower part.
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From June to August, the total number of influenza patients reduced to less than 500/week, and hence, this period is called the “inter-season” in this report. In the inter-season, the distribution of influenza patients among prefectures was totally random (Fig. 2A-2); the CC between the number of patients and population size was 0.382, 0.064, 0.056, 0.043, 0.159, and 0.063 in the years from 2010 to 2015, respectively. An interesting observation was that in the inter-season, influenza incidence was about 10-fold higher in Okinawa (indicated by an arrow) than in other prefectures. Okinawa is the southernmost prefecture of Japan.

Pandemic influenza: In 2009, AH1pdm2009 emerged in Mexico, spread worldwide, and was introduced in Japan in week 26 of the year; the influenza was classified as a “new infectious disease” under the Infectious Disease Control Law. All cases were reported mandatorily (Fig. 1A-2, circles). A plot of cumulative number of patients against prefecture population size is shown in Fig. 2B-1. The first patient reported under the law was the one reported in week 30 (1st week of the epidemic). In week 31 (2nd week of the epidemic), the CC was < 0.7, but in week 32 (3rd week of the epidemic), it was already > 0.7 and the slope was 1.13; in week 34, the slope decreased (slope: 0.68). Although the sequence of events was identical to that of the seasonal influenza, the epidemic progressed much faster than the seasonal influenza.

In week 35, AH1pdm2009 was excluded from the category of “new infectious diseases” on account of clinical symptoms that were almost indistinguishable from the seasonal influenza; thereafter, all the influenza cases, including those of AH1pdm2009, were reported from sentinel points (Fig. 1A-2, triangles) (http://www.mhlw.go.jp/kinkyu/kenkou/influenza/hourei/2009/08/dl/info0825-03.pdf). In the 2009/2010 season, 98% of the influenza virus isolates were of AH1pdm2009 (2). As shown in Fig. 2B-2 and in the right part of Table 1B, in week 41 (12th week of the epidemic), the cumulative number of patients reported from the sentinel points was already correlated (CC > 0.7) with population size, and the slope was as high as s = 1.4.

Measles and rubella: Measles and rubella are diseases that require notification of all the diagnosed cases. In 2008, when this rule was implemented, 11,013 cases were reported; however, owing to an intensified measles elimination program using the measles-rubella vaccine, the an-
Table 1. Correlation coefficients and slopes

| A: Seasonal Influenza 2001/2002–2014/2015 | 2001/2002 | 2004/2005 | 2007/2008 | 2010/2011 | 2013/2014 | 2014/2015 |
|----------------------------------------|-----------|-----------|-----------|-----------|-----------|-----------|
| Correlation coefficient                | 6th wk. (wk. 41) | 0.096 | 0.434 | −0.039 | 0.544 | 0.084 | 0.384 |
|                                       | 12th wk. (wk. 47) | 0.350 | 0.797* | 0.396 | 0.484 | 0.480 | 0.845 |
|                                       | 17th wk. (wk. 52) | 0.497 | 0.492 | 0.673 | 0.552 | 0.740 | 0.919 |
|                                       | 22nd wk. (wk. 5 next year) | 0.497 | 0.749 | 0.876 | 0.897 | 0.947 | 0.943 |
|                                       | 34th wk. (17 wk. next year) | 0.708 | 0.798 | 0.864 | 0.916 | 0.971 | 0.944 |
| Slope                                 | 6th wk. (wk. 41) | na | na | na | na | na | na |
|                                       | 12th wk. (wk. 47) | 1.078 | 1.647 | 1.599 | 1.198 | 1.114 | 1.208 |
|                                       | 17th wk. (wk. 52) | 0.886 | 1.396 | 1.245 | 1.031 | 0.917 | 1.193 |
|                                       | 22nd wk. (wk. 5 next year) | 0.773 | 1.156 | 0.851 | 0.921 | 0.971 | 0.819 |
|                                       | 34th wk. (17 wk. next year) | 0.747 | 0.767 | 0.732 | 0.895 | 0.895 | 0.788 |

Seasonal influenza cases reported from the sentinel sites. “Wk. 6th (wk. 41),” for example, indicates the data obtained from the patients accumulated from the 1st week of the epidemic (wk. 30) till the “6th week (wk. 41 of year).” The CC asterisked (2004/2005, 12th week) should be disregarded according to the criteria described in the figure legend for Fig. 1.

na, not applicable.

B: A/H1 pdm2009

| AH1pdm2009 | Influenza in 2009: sentinel reports | Weeks | Measles 2008 | Rubella 2012 | Rubella 2013 |
|------------|----------------------------------|-------|-------------|--------------|--------------|
| Correlation coefficient | wk. 30 (1st wk.) | 0.310 | wk. 41 (12th wk.) | 0.899 | 0.629 | 0.786 | 0.795 |
|                        | wk. 31 (2nd wk.) | 0.690 | wk. 47 (18th wk.) | 0.898 | 0.635 | 0.584 | 0.867 |
|                        | wk. 32 (3rd wk.) | 0.740 | wk. 52 (23th wk.) | 0.902 | 0.667 | 0.779 | 0.849 |
|                        | wk. 34 (4th wk.) | 0.710 | wk. 5 next year (20th wk.) | 0.907 | na | na | na |
| Slope                  | wk. 30 (1st wk.) | na | wk. 41 (12th wk.) | 1.416 | 0.907 | 0.911 | 0.902 |
|                        | wk. 31 (2nd wk.) | na | wk. 47 (18th wk.) | 1.011 | 0.850 | 0.845 | 0.852 |
|                        | wk. 32 (3rd wk.) | 1.130 | wk. 52 (23th wk.) | 0.850 | na | na | na |
|                        | wk. 34 (4th wk.) | 0.680 | wk. 5 next year (28th wk.) | 0.830 | na | na | na |

Cases reported as AHpdm2009 (left side column) and those reported from the sentinel points in 2009 (right side column). AHpdm2009: Wk. 30 (2nd wk.), for example indicates the data obtained from patients accumulated from 1st week of the epidemic (wk. 30) till the “6th week (wk. 41 of year).” Influenza in 2009/sentinel points: wk.41 (12th week) indicates week 41 of the year and 12th week after the start of the pandemic (week 30 of the year).

na, not applicable.

nual number of patients was reduced to 35 in 2015 (3). Measles and rubella epidemics exhibited a broad peak in April–June (Figs. 1B and 1C, respectively). Figs. 3A and 3B respectively show plots of the cumulative number of measles and rubella patients against prefecture population size. Table 1C summarizes the CCs between the number of patients and the population size and the slopes of the plots. Differently from influenza, the CC between the patient number and population size remained unchanged for measles (0.62–0.67) and for rubella (0.58–0.87) (Table 1C upper part) and the slope was close to 2 from the start to the end of the epidemic season (Figs. 3A and 3B; Table 1C lower part).

**Age structure in Japan:** For influenza, the correlation with $CC > 0.7$ between the number of patients and population size emerged earlier over the years (Table 1A): it emerged in the 34th week in 2001/2002, in the 22nd week in 2004/2005–2010/2011, in the 17th week in 2013/2014, and in the 12th week in 2014/2015. Before tackling the question of what may have caused this transition over time, we needed to check whether the used data faithfully represented the influenza epidemic with respect to age distribution in different prefectures, as the influenza data were sentinel-based and were under strong influence of choice of sentinel sites.

In Fig. 4A, the population sizes of different age groups (y) are plotted on the y-axis against total population size (x) on the x-axis for 47 prefectures in 2000 and 2014. Their relation could be expressed by an equation, $y = Ax^s$, where $s$ is the slope of the plot and $A$ is a constant. The plots run almost in parallel and the slopes were approximately 1 in 2000 and in 2014, indicating that the number of people belonging to different age groups was proportional to the prefecture’s population over time. As shown in Fig. 4B, however, in percentage, the age group of 15–34 yr was more and the age group of > 60 yr was less prevalent in populated urban prefectures than in less populated rural prefectures, i.e., the urban population was younger than the rural population. It was also found that the age group of 15–34 yr in 2001 reduced to below the plots of the age group of > 65 yr in 2015, reflecting the aging population of Japan.

Fig. 5A shows a plot of the number of influenza patients of different age groups (y) (Table 12-1: SENTINEL-REPORTING DISEASES (WEEKLY & MONTHLY) Number of cases and cases per sentinel by age group, sex, and prefecture-2013 in NESID database) on the y-axis.
Fig. 2. Relation between cumulative number of influenza patients and the population size at different periods after the epidemic start. Cumulative number of patients at different periods after the epidemic start was plotted in the y-axis against population size (×1,000) of prefectures. Both are in the logarithmic scale. Size of symbols was made larger with advancement of the epidemics (see explanations in the bottom of the figures). For years when zero case was 4 or less, the approximation was obtained by replacing 0 with 0.1; when there were more zero case prefectures, the plot was not done (indicated as “na” in Table 1A). A-1: seasonal influenza in 2001/2002–2014/2015. A-2: seasonal influenza during the inter-seasons in 2010–2015 (see the bottom of the figure for the time span). B-1: A(H1)pdm2009 reported as “new infectious disease” under the Infectious Disease Control Law. The first patient was reported in week 30. B-2: influenza patients reported from sentinel points in 2009.

Fig. 3. Relation between cumulative number of measles and rubella patients and the population size at different periods after the epidemic start. A: measles in 2008. B: rubella in 2012 and 2013. Week indicates week of the year. See figure legend of Fig. 2 for other information.
against the population size (x) on the x-axis. The relation could be expressed as $y = Bx^s$, where $s$ is the slope and $B$ is a constant. The plots run almost in parallel from 2000 to 2014, indicating that the sentinel sites were selected in a similar manner for all the prefectures over time. As shown in Fig. 5B, however, 70–80% of the data was derived from the age group of $< 14$ yr that occupied $\leq 15\%$ of the population (Fig. 4B).

It was indicated that despite the different percent distributions of the population’s age groups among prefectures (Fig. 4B) and the overrepresentation of the age group of $< 14$ yr in the influenza statistics (Fig. 5B), the relation between the number of influenza patients and the population size of different age groups remained almost unchanged over time. There was thus no indication of distortion of data that might have arisen from unbalanced selection of sentinel sites.

Close examination of Fig. 5A revealed that for all the age groups, the slope increased over the years, approaching 1, i.e., $s = 0.595–0.697$ in 2000, $s = 0.683–0.765$ in 2008, $s = 0.727–0.893$ in 2012, and $s = 0.789–0.944$ in 2014, i.e., the influenza incidence per population was relatively high in less populated prefectures in 2000, but became almost even in 2014. This indicated “homogenization” of the influenza epidemic among prefectures. This “homogenization” could have been responsible for the
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above-indicated earlier emergence of the correlation (CC > 0.7) between the number of influenza patients and population size in recent years (Table 1A). For further analysis of this phenomenon, we need weekly influenza data for different age groups that reflect their population size faithfully, ideally reporting all the cases. With demographic changes, infectious disease epidemiology will change, and previously chosen sentinels may become outdated in the near future.

DISCUSSION

For measles and rubella, the number of patients per prefecture was proportional to the square of prefecture’s population size from the start of the epidemic to the end (Fig. 3). The kinetics strongly suggested that measles and rubella spread through random, direct human-human contact, because the number of infected persons was expected to be proportional to the number of encounters between uninfected persons with infected persons, i.e., to N × pN, where N is the population size and p is the fraction of infected persons (1).

The spread of influenza was entirely different from that of measles and rubella. In the inter-seasons, patients were distributed randomly, but once the epidemic season began, the epidemic appeared in populated urban prefectures first and then spread nationwide, involving less populated prefectures. The plots of the number of influenza patients on the vertical axis versus population size on the horizontal axis resulted in straight lines with slope < 0.9 (Table 1A). Thus, influenza was almost population size-independent, while measles and rubella were strongly population size-dependent.

The difference between influenza and measles epidemics was also observed in the weekly incidence in individual prefectures. On one hand, the influenza epidemic continued without interruption, producing identically shaped plots for populated (Fig. 6A-1) and less populated (Fig. 6A-2) prefectures. On the other hand, similar plots for measles in the same year (2012) produced spiked plots (Fig. 6B-1) indicating frequent interruption of the virus spread. The spiked plots of measles were observed even when the number of the measles patients was much larger. In 2008, when 11,013 patients were reported, the plot pattern remained essentially the same (Fig. 6C), particularly in less populated prefectures (Fig. 6C-2). The spikes in the plots for measles were the “local infection clusters (LICs),” which were defined as “groups of patients re-

![Fig. 5. Age group distribution of influenza patients among prefectures. A: plot of number of reported influenza patients belonging to individual age groups in the y-axis against population size in the x-axis both in the logarithmic scale for year 2000, 2008, 2012, and 2014. B: plot of % influenza patient age group in the y-axis (ordinary scale) against population size in the x-axis (logarithmic scale) for year 2000 and 2014.](image)
ported from the same prefecture in successive weeks with at least 1 week of zero reporting before and after” (4). In view of the measles infection’s population size-dependency (1), LICs could be used as a surrogate of measles spread initiating from a single measles patient. Fig. 6D shows plots of LIC size on the y-axis against the rank number (starting from the largest cluster as number one) on the x-axis, which resulted in a straight line, i.e., LIC size distribution followed power distribution and was scale-free (5). When the epidemic was large, its y-axis intercept was high, and the slope was steep. When it was small, the y-axis intercept decreased and the slope also reduced (shrinkage of sizes of LICs). The distribution cannot be represented by a single number, like the reproduction number. This type of analysis was impossible for influenza, because the influenza infection continued without interruption during the season.

Although influenza and measles have often been described as airborne infections (6), the modes of transmission among the human population revealed above were widely different from each other.

**Conflict of interest** None to declare.

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