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Rurality and pandemic influenza: geographic heterogeneity in the risks of infection and death in Kanagawa, Japan (1918–1919)

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Abstract

Aim To characterise the impact of rurality on the spread of pandemic influenza by exploring both the numbers of cases and deaths in Kanagawa Prefecture, Japan, from October 1918 to April 1919 inclusive.

Method In addition to the numbers of influenza cases and deaths, population sizes were extracted from census data, permitting estimations of morbidity, mortality, and case fatality by 199 different regions (population 1.4 million). These outcomes were compared between four groups; cities (n=6), larger towns (38), smaller towns (101), and villages (54).

Results Whereas crude mortality in villages was lower than those of other population groups, the morbidity appeared to be the highest in villages, revealing significant difference compared to all cities and towns [risk ratio=0.601 (95% confidence interval: 0.600–0.602)]. Villages also yielded the lowest case fatality, the difference of which was statistically significant among four population groups (p=0.02).

Conclusion Rurality did not show a predictive value of protection against pandemic influenza in Kanagawa. Lower morbidity in the towns and cities is likely explained by effective preventive measures in urban areas. High morbidity in rural areas highlights the potential importance of social distancing measures in order to minimise infections in the event of the next influenza pandemic.

An increase in the number of outbreaks caused by highly pathogenic avian influenza type A (H5N1) virus in poultry, and its transmission in humans, has raised a considerable public health concern over the next pandemic.[1]

Although it is difficult to offer valid prediction of the forthcoming influenza pandemic, exploring previous pandemics is crucial for identifying specific patterns of transmission and suggesting optimal intervention strategies. Influenza caused by type A (H1N1) virus in 1918–19 is known to have caused the world's worst-known influenza pandemic, the so-called 'Spanish influenza' (which did not originate in Spain), causing an estimated 50 million deaths worldwide.

Quantification of the spread and transmission of pandemic influenza should provide valuable suggestions to improve the effectiveness of future pandemic preparedness plans.[2,3]

The mechanisms of transmission that may be deduced from the pattern of geographic spread of pandemic influenza have been demonstrated in several recent studies.[4–8] During the influenza pandemic it has been reported that severity (particularly mortality) differed considerably by geographic locations.[9,10]

Recently, historical data of Spanish influenza in New Zealand was revisited; it suggested that the mortality estimate was significantly smaller in rural areas than cities and towns.[11] Similarly, mortality has been suggested to be high in urban settings in other countries,[12,13] as supported by mathematical models attributing the differential mortality to sociodemographic conditions and public health measures.[14,15]

However, different epidemiologic outcomes have not been comparatively explored to examine the impact of rurality on 1918–19 influenza pandemic (e.g. infection and death). This is mainly owing to limited availability and scarce information of historical data which usually document the number of deaths alone. It is therefore fruitful to discuss this issue, explicitly distinguishing the implications of rurality between infection and death.

In the present study, we uncover a historical record of pandemic influenza in Kanagawa Prefecture, Japan, from October 1918 to April 1919, which precisely recorded both the numbers of cases and deaths by region. This study was aimed at characterising the impact of rurality on influenza by exploring three different outcomes—i.e. morbidity, mortality, and case fatality.

Methods

We extracted historical epidemiologic data of the influenza pandemic in Kanagawa, Japan, from 1918–19.[16] The historical data show numbers of cases and deaths in 199 different administrative regions; the total numbers between October 1918 and April 1919 were documented.

Prior to the pandemic, Kanagawa had suffered only sporadic outbreaks of bubonic plague at different times and places; thus it was believed that the prefectural government had been well trained and particularly successful in precisely tracing the spread of Spanish influenza in the prefecture.[16] In addition to influenza data, population sizes and mean household sizes (i.e. mean number of members per household) by region, as of the end of 1917, were obtained from a census report.[17]

Kanagawa is in the southern Kanto region of Honshu Island; and lies to the north between Yokohama and Tokyo. Ninety years ago the prefecture was very unique in that the capital city Yokohama played a key role as the major port of Kanto region; the main railway lines from Tokyo to southern Japan also passed through that city. Its population at the end of 1917 was 1,359,451, which covered 2415 km^2.

Detailed statistical record was independently summarised only in this prefecture in Japan, which was briefly revisited in a historical study introducing the report as containing the higher quality data.[18]

The present study used population size as a measure of assessing geographic heterogeneity. The populations were categorised as cities (population>20,000), larger towns (5,000<population≤20,000), smaller towns (2,000<population≤5,000), and villages (population≤2,000).

The cut-off values 2000 and 20,000 followed a previous study in New Zealand,[11] and 5000 was the minimum population size prerequisite to legally become a town as indicated by Japanese law.

Since we have access to cases, deaths and population sizes by region, morbidity (cases/population), mortality (deaths/population), and case fatality (deaths/cases) were comparatively examined.

- First, crude estimates of three outcomes were obtained by population group. These estimates were compared between groups using ratio of the outcome variables; i.e. incidence rate ratio (IRR), mortality rate ratio (MRR), and ratio of case fatality proportion (RCF).
- Second, distributions of the outcomes were compared between population groups, using one-way analysis of variance (ANOVA) followed by post-hoc test, employing Dunnett's method.

  When Dunnett's method was applied, villages were set as a control variable. Moreover, mean household sizes were similarly compared by population group, followed by test of within-group correlation by means of the Pearson's product-moment correlation between outcome variables and household size.

All statistical data were analysed using JMP v7.0 statistical software (SAS Institute Inc., Cary, NC, USA).

Results

In total, 292,139 cases and 5021 deaths were recorded during the period of observation, yielding overall morbidity, mortality, and case fatality estimates of 214.9 (95% confidence interval (CI): 214.2–215.6) per 1,000, 3.69 (3.59–3.79) per 1,000, and 1.72 (1.67–1.77)%, respectively.

Estimating the outcomes by region, median (25–75% quartile) morbidity and mortality were 182.7 (87.4–317.5) per 1,000 and 1.62 (0.84–3.06) per 1,000, respectively. Similarly, median (25–75% quartile) case fatality was estimated as 3.1 (1.6–5.1)%, ranging from 0 to 14.2%. Table 1 shows crude estimates by population group.

Table 1. Epidemiologic outcomes of influenza pandemic in Kanagawa, Japan: October 1918--April 1919

Population grouping (N)	Population (N)	Cases (N)	Deaths (N)	Morbidity† (95% CI‡)	Mortality† (95% CI‡)	Case fatality¶ (95% CI‡)
Cities (6)	634107	137028	2290	216.1 (215.1–217.1)	3.61 (3.46–3.76)	1.67 (1.60–1.74)
Larger towns (38)	319346	54901	1166	171.9 (170.6–173.2)	3.65 (3.44–3.86)	2.12 (2.00–2.24)
Smaller towns (101)	346034	79381	1366	229.4 (228.0–230.8)	3.94 (3.74–4.16)	1.72 (1.63–1.81)
Villages (54)	59964	20829	199	347.4 (343.5–351.2)	3.31 (2.86–3.78)	0.96 (0.82–1.09)

† Morbidity and mortality are calculated as rate per 1000 inhabitants for a period between October 1918 and April 1919; ¶Case fatality is proportion of deaths among the total number of cases; ‡ CI, confidence interval.

Morbidity was highest in villages, followed by smaller towns and cities. The risk of infection (measured as IRR) in all cities and towns was 0.601 (95% CI: 0.600–0.602) times that in villages. On the contrary, mortality was lowest in villages, and three other groups yielded a significantly higher estimate [MRR = 1.12 (1.11, 1.12)].

Case fatality was highest in larger towns followed by smaller towns and cities. Villages appeared to yield the lowest case fatality with an estimated 0.96 (0.82–1.09)%. Comparison of detailed ratios is summarised in Table 2.

In villages, crude estimates of mortality and case fatality were significantly lower compared to other population groups, whereas morbidity was significantly higher. Larger towns showed significantly higher case fatality [RCF=1.23 (1.18–1.29)] than smaller towns, but morbidity and mortality were significantly smaller in larger towns [IRR and MRR were 0.749 (0.744, 0.755) and 0.92 (0.89, 0.96), respectively].

Moreover, cities yielded higher morbidity [IRR=1.257 (1.253, 1.261)] than larger towns.

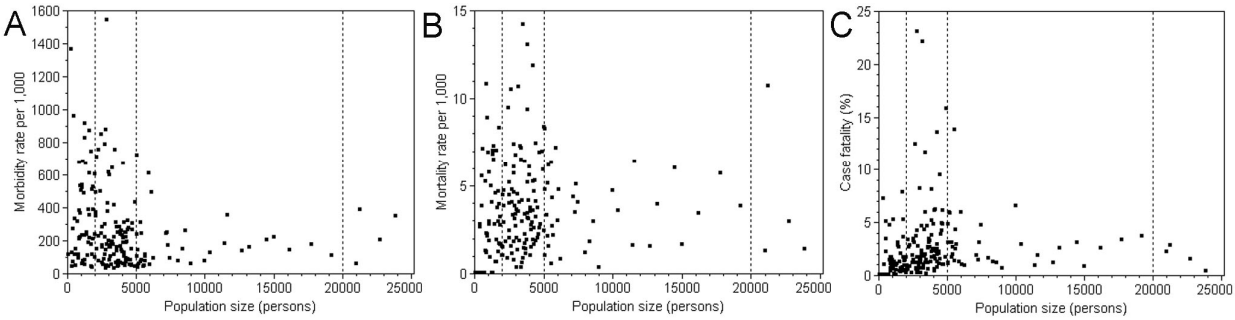
Within cities, the capital Yokohama showed significantly lower morbidity [IRR=0.990 (0.986, 0.993)] compared with five other cities. Within each group, we did not find any significant correlation between the outcomes and population size.

Table 2. Differential risks of influenza pandemic by population groups in Kanagawa, Japan, from October 1918--April 1919

Population grouping (N)	IRR† (95% CI‡)	MRR† (95% CI‡)	RCF† (95% CI‡)
Cities (6)	0.622 (0.621–0.623)	1.09 (1.08–1.10)	1.75 (1.73–1.77)
Larger towns (38)	0.495 (0.493–0.497)	1.10 (1.08–1.12)	2.22 (2.17–2.27)
Smaller towns (101)	0.660 (0.658–0.663)	1.19 (1.17–1.21)	1.80 (1.77–1.84)
Villages (54)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)

†IRR, incidence rate ratio; MRR, mortality rate ratio; RCF, ratio of case fatality proportions; ‡CI, confidence interval.

Figure 1. Morbidity, mortality, and case fatality of influenza pandemic as a function of population size, Kanagawa, Japan: October 1918--April 1919



Three outcomes (A) morbidity, (B) mortality and (C) case fatality of Spanish influenza pandemic are shown in relation to the population size. Each dot represents estimate of a single administrative region. In each panel, three vertical dashed lines represent cut-off values of population size for grouping (i.e. population sizes of 2,000, 5000, and 20,000). Yokohama (n=469,868) and Yokosuka (n=75,325) are excluded from the figure as the population sizes are large. Morbidity, mortality, and case fatality in these cities were 215.5 per 1,000, 3.74 per 1,000, and 1.73 % and 180.0 per 1,000, 2.4 per 1,000, and 1.33 %, respectively.

Figure 1 shows the distributions of the outcomes by population size and group. One-way ANOVA revealed that morbidity was significantly different between population groups (p=0.01), where villages appeared to have experienced significantly higher morbidity than larger towns (p<0.01). Mortality did not differ significantly between

population groups (p=0.33), but we found a significant difference in case fatality (p=0.02) between the groups.

Following the post-hoc test, smaller towns appeared to yield higher case fatality than villages (p=0.01). Unlike the observation using the crude case fatality, case fatality in larger towns was not significantly different from that of villages (p=0.12).

Mean household size significantly differed by population group (p<0.01), which was characterised by significantly smaller household sizes in cities (p<0.01) and larger towns (p=0.02). However, we did not find any significant within-group correlations between mean household size and morbidity as well as mortality.

Discussion

The present study analysed differences in the risks of infection and death of Spanish influenza by population size. Using historical data in Kanagawa, Japan, the numbers of cases and deaths as well as population size were extracted, enabling us to analyse three different outcomes.

To the best of our knowledge, this study is the first to investigate geographic differences in morbidity, mortality, and case fatality, explicitly separating the role of outcomes. Although our case fatality estimates were smaller than those of hospitalised cases among young adult armies in Tokyo,[19] the higher estimate in the hospital most likely highlights more severe cases (i.e. those who were hospitalised) and age (i.e. young adults who were at high risk of death), and our estimates are consistent with that of entire Japan ranging from 0.5–13.7 % with the mean estimate of 1.0%[20] (mortality and morbidity estimates for all prefectures in Japan are given in English in p. 397 of Rice and Palmer[21]).

With regard to crude mortality estimates by population group, MRRs were smaller than those in New Zealand,[11] but the consistent pattern was seen with lowest estimate in villages and highest in smaller towns. However, morbidity was highest in villages. Case fatality proportion bridges the relationship between morbidity and mortality, and villages appeared to yield the lowest estimate, which was significantly different by population group in both comparisons of crude estimates and the corresponding distributions by region.

In other words, the low mortality in villages appeared to be greatly influenced by case fatality, the conditional probability of death given infection (or onset), at least in the unique dataset of Kanagawa. Moreover, when we comparatively examined the distributions of mortality using ANOVA, no significant difference in mortality was found by population group. That is, although our analysis of crude mortality by population group implied a possible protection of the population by remoteness, the difference reflected differing fatality of disease by region, and rather, morbidity appeared highest in villages.

Kanagawa was one of the prefectures where the administrative regions were moderately affected by the influenza pandemic.[21] In a location where extreme remoteness may not be expected,[22] geographic heterogeneity in the risk of infection (i.e. morbidity) revealed opposite pattern of our expectation, showing higher risks of infection in smaller population groups.[14]

Although the data in Kanagawa differs from that of New Zealand in aspects such as the time period and areas of observation, the present study suggests that rurality was not predictive of protection against pandemic influenza when we measured both morbidity and mortality. Considering the similar variations between smaller and larger towns, larger towns showed lower morbidity than smaller towns, and accordingly, smaller towns were also not protected from infection in Kanagawa.

It is difficult to intuitively suggest the definitive reasons why significantly high incidence was seen in villages. Mean household size tended to be higher as population size decreases, but this was not correlated with the risk of infection. Heterogeneous patterns of transmission would not be clarified unless the relevant social and biological backgrounds are explicitly clarified.

As a potential mechanism of intensive within-regional transmission in rural areas, it should be noted that each village was a small community of farmers who lived closely together and were well-connected to each other, and perhaps, this permitted the spread of the disease once the community experienced the introduction of an influenza case.

In practical terms, in order to minimise the risk of infection, high morbidity in rural areas highlights importance of social distancing measures in the event of the forthcoming next pandemic. Provided that rural areas are at high risk of transmission, and given that communities in the present day are more densely connected to each other than those in 1918–19, it would be critically important to protect the community from interregional introduction of cases.

If rural areas indeed prevent themselves from inter-regional introduction of cases by means of social distancing, it will be possible to expect lower risk of infection in these areas.

In addition, towns and cities could have been potentially protected against influenza due to population and individual countermeasures.[18,23] Indeed, public health authorities in Kanagawa were better-prepared for an epidemic than almost any other prefecture in Japan.[24] For example, spinning (cotton) mills in Kanagawa initially suffered from outbreaks in October 1918 and thus the prefecture decided to close similar factories and restricted the movements of individuals in crowded dormitories at an early phase of the pandemic.[16]

The prefecture was also a leader in warning the public of the dangers of influenza and its mode of transmission through the use of pamphlets and posters.[20,24] At the individual level, the use of several different types of mask was recommended not only for those participating in medical practices but also the general population.[20,25]

Mathematical analysis of Spanish influenza data in the US suggests not only that intervention effectively reduced the disaster size, but also that individuals reactively reduced the number of infectious contacts, perhaps by behavioural changes.[14]

Morbidity and mortality with time and place in addition to any information of the timing of implementing public health measures would permit explicit analyses of the effectiveness of countermeasures. To achieve precise estimation of the effectiveness, it is essential to address heterogeneous contact patterns and risk of severe manifestations, and thus further studies are needed to precisely estimate the impact of interventions in heterogeneously mixing populations with varying risks of death.

How about the lower case fatality in villages than in other locations? As a possible reason, differential case fatality could be explained by different levels of previous exposures. A historical study suggests low frequency of previous exposures in town areas by previous pandemic of type A (H1N1) influenza.[18] The similar argument of the impact of acquired immunity on the risk of influenza death (i.e. partial protection) has been made historically.[26] However, if this was the case, not only the risk of death but also that of onset (given infection) should have been more or less inhibited by previous exposure in villages.

In line with this, age-related heterogeneity and underlying diseases have to be remembered as factors generating heterogeneous risks of death. We postulate that some underlying diseases and sociodemographic characteristics have modified case fatality, which in general varies widely by region.[10,27] For example, it is likely that proportion of young adults were higher in cities and towns than that in villages where middle-aged farmers constituted the core of rural population. Moreover, as a potential reason, poorer health and nutrition in towns and cities as well as limited social supports and healthcares in urban areas (e.g. limited nursing care offered by neighbours) could have also contributed to higher case fatality in urban areas.

Further data on socioeconomic status could be useful in testing whether poverty levels in urban areas contributed to higher case fatality than in rural areas.

A limitation must be noted in relation to the interpretation of morbidity and case fatality. If historical survey included many false diagnoses of influenza (e.g. febrile illness caused by different disease), disease misclassification (i.e. non-differential misclassification) must have been present.

Although the historical record in Kanagawa explicitly documents clinical pictures of influenza with the characteristic flu-like symptoms (e.g. fever, myalgia, severe malaise),[16] it is fairly difficult even today to achieve population-based diagnoses of influenza with high sensitivity and specificity. Therefore, if the diagnoses of cases in rural areas included more false negatives than those in cities, reported estimates of morbidity and case fatality in rural areas might be deemed, respectively, overestimate and underestimate, which cannot be fully addressed using the historical record of Spanish influenza alone. Besides, as we briefly discussed, the prefecture had suffered from plague outbreaks prior to the pandemic, and Kanagawa was one of the prefectures where the epidemiologic data by region were most precisely recorded in Japan.

It is worth documenting that agreement between pneumonia and influenza death with time were visually and implicitly examined in the original report.[16] Also, it should be remembered that it is not rare to observe that the regional pattern of influenza morbidity goes in the opposite direction to that of mortality.[28]

As another technical issue, the present study did not account for other variables except for population size. Investigations over age and gender would be desirable, and analyses of similar data in other locations are called for. In particular, historical record in a geographically isolated area (e.g. small island) with both the numbers of cases and deaths has a potential to inspire new knowledge to the world on this issue.

As an epidemiologic implication, the present study would be deemed typical to indicate the critical importance in explicitly distinguishing the roles of outcomes (e.g.

infection and death).[28] It is usually the case that we can obtain death data alone from historical literature. If this is the case, the underlying assumption to make an interpretation and its validity would play key roles to offer valid conclusions.

Specifically, although mortality data are frequently used even for performing predictions,[29] it should be noted that mortality reflects two separate epidemiologic steps (i.e. infection and death) which are differently modified by numerous factors. To decipher the mechanisms of transmission using death data only, some reasonable adjustment or additional case data are needed.

So, weren't rural areas protected against pandemic influenza? Unfortunately, the present study cannot offer explicit general conclusion on this issue. At least, our analysis of the data in Kanagawa suggests high incidence in rural areas, and in this prefecture rural areas were not protected from pandemic influenza in terms of both mortality and morbidity.

Our result was suggestive of potential protectiveness of individuals in rural areas from severe disease (i.e. death given infection), but it has to be clarified more in detail with other variables.[30] Accordingly, the potential importance of social distancing (to minimise the risk of infection) and an epidemiologic need in measuring different outcomes were highlighted. Further studies with different datasets measuring both the numbers of cases and deaths are therefore crucial.

In addition, mathematical and statistical models with spatiotemporal components can be useful tools for deciphering the mechanisms of observing different outcomes by region.

In conclusion, the present study analysed the role of rurality during the 1918–19 Spanish influenza pandemic in Kanagawa, Japan, using numbers of cases and deaths by region. Villages had the highest reported incidence.

If the geographic patterns of morbidity were valid, lower morbidity in the towns and cities might be potentially explained by effective preventive measures in urban areas. However, provided that morbidity data were not sufficiently accurate, slightly smaller estimates of mortality in rural areas still imply the potential protectiveness of remote areas.

In future studies, high resolution spatiotemporal morbidity and mortality data in addition to any information on the timing of public health measures would be crucial for offering the most effective pandemic preparedness plans in heterogeneously mixing populations with varying risks of severe manifestation.

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