Statistical analysis of influenza propagation pattern using prescription data from Tochigi Prefecture

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Abstract:

In this study, we estimate the propagation patterns of influenza using prescription data obtained from pharmacies in multiple areas. In our model, we assume that a peak in the volume of sales of medicine corresponds to a peak in an influenza epidemic, and we use a cross-correlation function to estimate propagation patterns by estimating the interregional gap in the time-series of the volume of sales of anti-influenza medicine. We also examine the causal relation between different time-series using the Granger causal test. Based on the propagation patterns estimated from these causal relations, we determine that the influenza virus consistently spreads outward from city centers. Finally, we assess the reproducibility of results obtained from the two estimation methods used in this study using a stochastic SIR model.

Keywords

influenza propagation; cross-correlation function; Granger causality test; anti-influenza; SIR model.

1. Introduction

Most epidemiological studies use data obtained from medical institutions. While such data primarily comprise direct patient information, such as medical records, they often also contain indirect information, such as prescription records. In this study, we estimate the propagation patterns of infectious diseases, particularly influenza, using prescription data.

The estimation of the progress and dispersion of infectious diseases is important in the field of epidemiology because disease propagation estimates can be used to prevent their further expansion. An early reference is John Snow's study (1849) of the infection route of cholera. More recently, the National Institute of Infectious Diseases has begun to collect data from about 5,000 medical institutions on the number of patients reporting specific diseases per week. These figures are plotted by prefecture and the results are made public. Sugawara *et al.* (2011) proposed that early detection of chickenpox epidemic is possible by tracking changes in the sale of the axilobil

preparation because this formulation is highly likely to be prescribed to patients with suspected chickenpox. In another study, Sugawara *et al.* (2007) suggested the possibility of uncovering influenza epidemic one to three weeks earlier by analyzing data on the volume of sales of combination cold remedies in pharmacies. In another study, Ijuin *et al.* (2006) determined the infection route and speed of influenza propagation between distant sites by calculating the cross-correlation between daily variations in the amount of drug sales at pharmacies in Tokyo and the surrounding region.

In this study, we focus only on the volumes of sales of anti-influenza medicines for which a prescription is necessary: these include Tamiflu capsules, Tamiflu dry syrup, Innabir, and Relenza. As a document necessary for a patient to purchase a controlled medicine, a prescription includes information such as the type and amount of the medicine prescribed and cannot be obtained without a medical examination. Thus, only a person with a diagnosis of influenza is able to purchase the medicines listed above, and we can regard the volume of sales of anti-influenza medicines as a proxy for the number of influenza patients. As the peaks of the time-series data on the volume of sales of the anti-influenza medicines assessed in this study differ by region, we hypothesized that estimating the respective peak gaps would allow us to model the propagation patterns of influenza.

Specifically, the purpose of this study was to estimate influenza transmission patterns in Tochigi Prefecture by analyzing the sales volumes of anti-influenza medicines in 26 pharmacies in the prefecture. In the next section, we describe our data. Then, in Section 3 we describe the method we used to estimate by the cross-correlation function. In Section 4 we describe an alternative estimation method based on Granger causality tests. In Section 5, we attempt to determine the contagion mechanism necessary to produce the observed pattern of an epidemic wave using a stochastic SIR model. Finally, we present our conclusions and discuss future work in Section 6.

2 Data

2.1 Data of analysis object

The data analyzed in this study comprised the sales volumes of anti-influenza medicines at 26 pharmacies in Tochigi Prefecture, which is located in the northeast suburbs of Tokyo and had a population of 1,974,720 people as of 2015. The prefectural capital is Utsunomiya city, which had a population of 519,934 as of 2015.

The data represent prescriptions filled from November 1, 2011 to April 29, 2012, November 1, 2012 to April 30, 2013, and November 1, 2013 to April 30, 2014; we call these periods the first, second, and third seasons, respectively.

2.2 Area

We did not estimate propagation patterns of influenza between pharmacies; instead, we divided the 26 pharmacies into 10 categories based on location and estimated propagation patterns between the localities, which are shown in Table 1 below.

Table 1: Groupings of pharmacies by area

Area	Population	Number of pharmacies
A (Oyama City)	166,593	4
B (Around Shimono City)	60,135	4
C (Utsunomiya City)	521,820	7
D (Ohata City)	72,892	2
E (Nasushiobara City)	118,308	1
F (Tochigi City)	163,536	1
G (Moka City)	80,907	2
H (Haga Town)	15,955	1
I (Kanuma City)	99,949	3
J (Nasukarasuyama City)	28,005	1

2.3 Moving average

We smoothed the data using a moving average with a window of seven days as the raw data on volumes of sales of anti-influenza medicines zeroed out at regular intervals owing to recurring fixed pharmacy closure dates, which we believed would have affected the analysis results.

3. Estimation by the cross-correlation function

The influenza epidemic periods differed by locality. Based on our assumption that the volume of sales of medicine tracked these periods, we could use the differences in sales patterns to estimate how the timing of epidemic periods varied by location and thereby model the propagation patterns of influenza.

As described above, we believed that the pharmacy-specific data from the Tochigi prefecture could be used as indicators of epidemic progress by area. To clarify the gaps between the respective area time-series, we used a cross-correlation function. The general cross-correlation function between two time-series, x and y , is defined as

$$r_{\tau} = \frac{\sum_{i=1}^{n-\tau} (x_i - \bar{x})(y_{i+\tau} - \bar{y})}{\sqrt{\sum_{i=1}^{n-\tau} (x_i - \bar{x})^2} \sqrt{\sum_{i=1}^{n-\tau} (y_{i+\tau} - \bar{y})^2}}, \quad (1)$$

where $\bar{x}$ and $\bar{y}$ denotes the mean over time t and τ is the lag. Equation (1) has a maximum when the correlation between x_i and $y_{i+\tau}$ is at a maximum among all possible τ ; therefore, equation (1) is a function of τ .

3.1 Methodology

We calculated the cross-correlation function for all combinations of pharmacies, $a - n$, for each season. As an example, the results for the first season, showing the gaps between the time-series of anti-influenza medicine sales at all pharmacies, are shown Table 2. To refine the example, we examine pharmacies b and d in the table. The calculated cross-correlation coefficient between the respective time-series of these pharmacies has a maximum at $\tau = 8$ days; in other words, the coefficient of correlation is maximum (or minimum) when the time-series are shifted relative to each other by eight days. In this case, this indicates that pharmacy d 's anti-influenza medicine sales volume peaked earlier than those of pharmacy b .

The "average" column includes the means of the time lags between a fixed pharmacy X (the rows of the lag matrix) and each of the other pharmacies Y (the columns of the lag matrix). These mean lags can be regarded to indicate the relative order of infection, and we posit that the highest value in the mean column corresponds to the earliest pharmacy to "experience" the infection. In Table 2, pharmacy y has the highest mean lag value; thus, the delays of onset of infection at other pharmacies can be determined by the differences in the respective mean lag values from that of pharmacy y .

The "gap" column lists the gaps in epidemic onsets relative to that of pharmacy y . To estimate the propagation pattern of influenza among the localities, we calculated the means of the relative values and then the relative lags by locality.

Table 2: First season lag matrix

		Y								Average	Gap
		<i>A</i>	<i>b</i>	<i>c</i>	<i>d</i>	<i>e</i>	<i>f</i>	...	<i>y</i>		
X	<i>a</i>	0	0	-5	-8	15	2	...	-15	-1.00	14.52
	<i>b</i>	0	0	2	8	17	5	...	-14	1.92	11.60
	<i>c</i>	5	-2	0	3	20	10	...	-16	3.48	10.04
	<i>d</i>	8	-8	-3	0	-8	9	...	-7	1.68	11.84
	<i>e</i>	-15	-17	-20	8	0	0	...	7	-4.52	18.04
	<i>f</i>	-2	-5	-10	-9	0	0	...	-18	-5.40	18.92
	<i>g</i>	-1	-1	-7	-7	5	2	...	-15	-3.24	16.76
	⋮	⋮	⋮	⋮	⋮	⋮	⋮	...	⋮	⋮	⋮
	<i>y</i>	15	14	16	7	-1	18	...	0	13.52	0.00

3.2 Result of estimation using cross-correlation function

From the cross-correlation results, for all seasons the average lag values for nearly all pharmacies located in Area C are higher than those in all other areas. In other words, the peak prescription days in Area C pharmacies are mostly earlier than those in other areas. Based this result, we can posit that the influenza epidemic spread from Area C.

4. Estimation using the Granger causality test

The Granger causality test is a method for detecting causal direction between two time-series data sets. The test detects correlation between the current value of a time-series and the past values of another time-series. We used the Granger test in this study to determine whether the current number of prescriptions in Area X is influenced by the past number of prescriptions in Area Y; if this is so, we can reasonably conclude that influenza propagated from Area Y to Area X.

4.1 The Granger causality test

To implement the Granger causality test, a vector auto-regressive model of two variables, x and y , and a constant term is employed using the following model:

$$x_t = \alpha_1 + \sum_{i=1}^k \beta_{1t} x_{t-i} + \sum_{i=1}^k \gamma_{1t} y_{t-i} + \varepsilon_{1t}, \quad (2)$$

$$y_t = \alpha_2 + \sum_{i=1}^k \beta_{2t} x_{t-i} + \sum_{i=1}^k \gamma_{2t} y_{t-i} + \varepsilon_{2t}, \quad (3)$$

where α is a constant term, β and γ are regression coefficients, and ε is an error term.

According to expression (2), a necessary and sufficient condition for a lack of causation from y to x , as denoted by the Granger formulation ($y \nrightarrow x$), is $\gamma_{11} = \gamma_{12} = \dots = \gamma_{1k} = 0$. Thus, the null hypothesis (H_0) and the alternative hypothesis (H_1) are determined respectively as follows:

$$\begin{aligned} H_0 : \gamma_{11} = \gamma_{12} = \dots = \gamma_{1k} &= 0, \\ H_1 : \text{for eather } i; \gamma_i &\neq 0. \end{aligned}$$

The F -test is used under H_0 as estimated based on the least-squares method under γ_{1k} in expression (2); it is furthermore assumed that the residual sum of the squares is “RSS.” We can then estimate expression (2) using the least-squares method and assume that the residual sum of the squares is “USS.” The F -value can then be calculated as

$$F = \frac{(RSS - USS)/k}{USS/(T - 2k)}, \quad (4)$$

where T denotes the number of data points and k is the order. The null hypothesis may be dismissed if the F -number degree of freedom ($k, T - 2k$) is larger than the critical value of the level of significance (5%), in which case there would be an expectation of causation from y to x ($y \rightarrow x$).

4.2 Result of estimation by the Granger causality test

The Granger causality results are shown in Tables 4, 5, and 6, in which the circles indicate that Granger testing between Areas X and Y produced significant results. For example, the causality testing between Areas A and B produced significant results, i.e., the current number of prescriptions in Area B is linked to the past number of prescriptions in Area A. From this, we can conclude that influenza propagated from Area A to Area B. Examining the results for Areas A and B in the tables, we see that the indicated causality relation in the third season differs from that in the first two, from which we can see that both areas can originate the spread of influenza under an interactive causation model, a result that we believe stems from confounding factors. We then compared the Granger causality test results with those produced using the cross-correlation function. As noted in 3.2 above, the cross-correlation results suggest contagion emerging from Area C and spreading to the other areas. By contrast, a much less significant causal relation emerges from the Granger results, with Area C being the destination of

contagion from all of the other areas. In other words, under the Granger model the results were opposite to the results of the cross-correlation function in terms of direction of spread. However, as Area C is consistently “infected” under all Granger causality test results, and can ultimately estimate them within Area C whenever influenza patients exist. In other words, influenza is always prevalent within Area C during any given season, and it can be reasonably concluded that it originally spreads from there to neighboring areas.

Table 3: The results of the Granger causality test for the first season

1st season		effect									
		A	B	C	D	E	F	G	H	I	J
Cause	A		○	○							
	B	○		○	○			○			
	C	○	○					○			
	D	○	○	○				○			
	E	○	○	○	○			○		○	
	F			○	○				○	○	
	G		○	○	○					○	
	H	○	○	○	○		○	○		○	
	I		○	○	○	○		○			
	J	○		○			○		○	○	

Table 4: The results of the Granger causality test for the second season

2nd season		effect									
		A	B	C	D	E	F	G	H	I	J
Cause	A		○	○	○	○	○	○		○	
	B	○		○				○		○	
	C		○			○		○		○	
	D	○	○	○		○		○		○	
	E	○	○	○	○		○	○		○	○
	F	○	○	○	○	○		○	○	○	○
	G	○	○	○	○		○		○	○	○
	H	○	○	○	○	○	○			○	○
	I	○	○	○		○	○	○			
	J	○	○	○	○		○	○	○	○	

Table 5: The results of the Granger causality test for the third season

3rd season		effect									
		A	B	C	D	E	F	G	H	I	J
Cause	A			○	○			○			
	B			○						○	
	C		○					○		○	○
	D		○	○		○		○		○	○
	E	○		○				○			
	F	○	○	○	○			○	○	○	
	G	○	○	○	○		○			○	
	H	○	○	○	○	○		○		○	○
	I	○	○	○							
	J	○	○	○	○			○		○	

5. Simulation and contagion mechanism

Our analysis of the medicine sales time-series showed a tendency for epidemics to first arrive in the largest Tochigi prefecture city, Utsunomiya, before spilling over to the surrounding cities. In this section, we use a stochastic SIR model [9] to determine which contagion mechanism best explains this order of epidemic wave arrival and propagation.

5.1 Simulation model

The original version of the SIR model splits a target population into three compartments—the susceptible, infected, and recovered populations—and describes changes in their respective numbers (denoted at time t by $S(t)$, $I(t)$, and $R(t)$, respectively) in terms of ordinary differential equations:

$$\frac{dS(t)}{dt} = -\beta \left(\frac{I(t)}{N} \right) S(t), \quad \frac{dI(t)}{dt} = \beta \left(\frac{I(t)}{N} \right) S(t) - \gamma I(t), \quad \frac{dR(t)}{dt} = \gamma I(t).$$

Here β is the transmissibility parameter and $1/\gamma$ is the mean infection period. The model describes the transit of individuals between compartments in a manner analogous to chemical reactions under the assumption of an equally mixed target population.

Here, we employ an extended version of the SIR that incorporates spatial structure (because we are interested in the order of epidemic arrival by city) and stochasticity (because spillover from one city to another is likely to occur by chance). Splitting each of compartments and distinguishing them with a suffix by city ($S, I, R \rightarrow S_i, I_i, R_i$) suffices to achieve spatial differentiation. To add stochasticity, deterministic descriptions of changes in populations are replaced with samples from binomial distributions. We then have the following adjusted model:

$$S_i(t) = S_i(t - \Delta t) - \Delta[S_i \rightarrow I_i]$$

$$I_i(t) = I_i(t - \Delta t) + \Delta[S_i \rightarrow I_i] + \Delta[I_i \rightarrow R_i]_i$$

$$\Delta[S_i \rightarrow I_i] \sim \text{Bin}\left(S_i, \beta \frac{I_i + \sum_{j \neq i} \epsilon_{ij} I_j}{N_i} \Delta t\right),$$

$$\Delta[I_i \rightarrow R_i] \sim \text{Bin}(I_i, \gamma \Delta t).$$

Beta, the transmissibility coefficient, is chosen so that reproduction number $\mathbf{R}_0 := \beta/\gamma$ is 1.3 (the reproduction number is the mean number of secondary cases owing to a single infected case when the target population is fully susceptible), and the mean infectious period $1/\gamma = 3$ days. The parameter epsilon controls the degree of influence from other cities on the reproduction of infectious cases. We assume a decreasing function with respect to the distance between cities on ϵ with a scale parameter ϵ_0 :

$$\epsilon_{ij} = \epsilon_0 \left(\frac{d(i, j)}{d_0} \right)^{-\alpha},$$

where the distance $d(i, j)$ between city i and city j and the parameters d_0 , α , and ϵ_0 are estimated from data. A power-law dependence on the distance is often assumed to describe the spatial spread of infectious disease using a simple model (2001), (2005).

5.2 Empirical construction of Likelihood function

Spearman's rank-order correlation of the arrival times to five cities in Tochigi prefecture (Oyama, Shimotsuke, Utsunomiya, Ohtawara, Kanuma) between two of 11/12-, 12/13- and 13/14-seasons shows that influenza wave arrived each city almost at random time (the correlation spans -0.13 to 0.23, Table 6), while it lasted every year a similar number of days there once has arrived. We have applied to a procedure similar to our earlier work (2016), in order to define the arrival time and the epidemic period of each city and to calculate rank-order correlations.

The rank-order correlation and the epidemic period just characterize the entire epidemic, and hence it is difficult to connect directly data and the output of our mechanistic model via some likelihood function written in a closed form. We then carry out simulations for a set of parameter configures to empirically construct likelihood function as a histogram, where 128 runs with different random number seeds are carried out for one parameter setting. Formally, the likelihood function is written in the form,

$$L(\theta) = p(\text{RC}^{(11,12)} | \theta) p(\text{RC}^{(12,13)} | \theta) p(\text{RC}^{(11,13)} | \theta) \times \prod_{y \in \{11, 12, 13\}} \prod_{g \in \{A, B, C, D, I\}} p(\tau_g^y | \theta),$$

where the parameters that are to be estimated are denoted by $\theta \equiv (\epsilon_0, N_1, d_0, \alpha)$, the factor related to the rank-correlation is $p(\text{RC} | \theta)$, and the factor related to the epidemic period is $p(\tau_g | \theta)$ for each region $g \in \{A, B, C, D, I\}$.

Table 6: The rank-correlation of arrival times to cities in Tochigi prefecture, Oyama, Shimotsuke, Utsunomiya, Ohtawara, and Kanuma between two of 2011/12-, 12/13- and

13/14-seasons		
	2012/13	2013/14
2011/12	0.23	-0.13
2012/13	-	0.074

5.3 Simulation results

We carried out simulations over the parameter ranges $d_0 \in \{1, 2, 5, 8, 10\}$, $\alpha \in \{1.5, 1.8, 2.0\}$, and $\varepsilon_0 \in \{0.001, 0.005, 0.05, 0.1\}$. The distributions at the maximal likelihood ($\varepsilon_0 = 0.005$, $N_1 = 896$, $d_0 = 5\text{km}$, $\alpha = 1.5$) of rank-correlation and epidemic period are shown in Figs. 1 and 2, respectively. All three rank-correlation values calculated from the data are lower than the mean. Our modeling may therefore assume a connection between cities that is tighter than reality, although further observations are required for a definitive answer. Although the modeled epidemic durations are all coincident with the mode, their distribution is long-tailed, indicating that our model may yield greater uncertainty than actually occurs. Considering only the epidemic period as a measure of goodness of fit results in a distribution concentrated toward the shorter values. An example of such a configuration is shown in Fig. 3, in which the parameters are chosen so that the only factor $p(\tau_g|\theta)$ of the likelihood is maximized with respect to the first season dataset. However, the rank-correlation takes much higher values, which is not consistent to the results in the actual epidemic.

 Figure 1. Distribution of the rank-correlation $p(\text{RC}|\theta)$ at the maximal likelihood.

Figure 2. Distribution of epidemic period $p(\tau_g|\theta)$ at the maximal likelihood.

Figure3. Distribution of $p(\tau_g|\theta)$ at the maximal likelihood with respect to $p(\tau_g|\theta)$ and the first season data set.

6. Conclusion and Future work

This study focused on the change in time of the volume of sales of anti-influenza medicines in Japan's Tochigi Prefecture to estimate the direction of the spread of influenza. To enact our analysis, we used both the cross-correlation function and the Granger causality test, with both analytical approaches yielding results that consistently indicated the spread of influenza from Area C to outlying areas. However, the speed of this spread remained undetermined. Moreover, we need to further verify the results of our Granger causality test.

We then attempted to reproduce the results obtained from the respective estimation methods using a stochastic SIR model, but found that a more accurate reproduction required more data than was used in this study.

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