Geographical Pattern of Influenza Propagation in Tokyo and Its Neighborhood in Three Seasons

Tsuyoshi Kobari,[a,f] Sumiko Kondo,[b] Hidekazu Tanaka,[b] Kazushige Ijuin,[c] Hisako Takeuchi,[d] Hiroyasu Sato,[e] Kazuo Iwaki,[e] Fumiyoshi Ishii,[f] Rieko Matsuda,[g] Yuzuru Hayashi,*,[g] and Takehiko Yajima[h]

[a]Kosumo Chouzai Yakkyoku Co., Ltd., 2–129–3 Miyahara, Kita, Saitama, Saitama 331–0812, Japan, [b]Pinokio Pharmacy Co., Ltd., 8–21–14 Youtou, Utsunomiya, Tochigi 321–0904, Japan, [c]Tanashi Yakuhin Co., Ltd., 4–25–5 Tanashi, Nishi-Tokyo, Tokyo 188–0011, Japan, [d]Triad Japan Co., Ltd., 2–18–10 Kitasato, Sagamihara, Kanagawa 228–0829, Japan, [e]School of Pharmaceutical Sciences, Ohu University, 31–1 Misumido, Tomita-machi, Koriyama, Fukushima 963–8611, Japan, [f]Department of Pharmaceutical Sciences, Meiji Pharmaceutical University, 2–522–1 Noshio, Kiyose, Tokyo 204–8588, Japan, [g]National Institute of Health Sciences, 1–18–1 Kami-Yoga, Setagaya, Tokyo 158–8501, Japan, and [h]Faculty of Pharmaceutical Sciences, Toho University, 2–2–1 Miyama, Funabashi, Chiba 274–8510, Japan

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The aim of this paper is to compare the geographical routes and speeds of influenza propagation in and around Tokyo, including Kanagawa, Saitama, Tochigi and Fukushima prefectures, in the seasons of 2003/2004, 2004/2005 and 2005/2006. Each season ranges from November 1st to October 31st. The propagation pattern is estimated from the daily variations in the sales amount of anti-influenza drug at about 30 pharmacies in the area. The time lags (day) of influenza infection periods between distant pharmacies are calculated by the cross-correlation functions of the drug sales at the pharmacies. We conclude that the influenza infection spread from the urban area of Tokyo to its suburbs (Saitama and Kanagawa) along the railway systems in all the seasons examined. However, no definite infection routes can be found in Tochigi and Fukushima. The infection periods of adults are contrasted with those of children in individual observation sites.

Key words —— pharmacy, influenza, anti-influenza drug, bioterrorism

INTRODUCTION

The geographic propagation of disease in human as well as other populations has been a matter of great interest especially in the area of epidemiology[1–12] and methods for geographically recognizing the propagation have been developed such as choropleth maps and geographic information systems.[1–7]

Recently, a new method for estimating the route and speed of influenza propagation was put forward.[13–15] The most prominent features of this method are the mathematical technique and sources of disease information. The fundamental assumption is that the health conditions of people are reflected by the drug sales at pharmacies.[13,14] In the previous paper,[15] the time series of drug sales were collected from fourteen community pharmacies and analyzed with the cross-correlation function. The study led to the conclusion that the influenza infection appears to have spread from the urban area of Tokyo to its suburbs at an averaged speed of 3.5 km/day in the period from November 1st, 2004 to October 31st, 2005 (04/05 season).[15]

The previous study[15] examined only one season of influenza infection and the interesting question remains whether the radial routes from Tokyo to suburbs can apply to other seasons. Similarly, the invariability of the infection speed (3.5 km/day) has yet to be studied in other seasons. From the epidemiological viewpoints, a wider region of the pharmacy network including rural areas need also be taken into account.

The aim of the present paper is to study the routes and speeds of influenza propagation in Tokyo and its neighborhood in the seasons of 03/04, 04/05 and 05/06. The target geography includes the big city (Tokyo), suburbs (Saitama and Kanagawa) and

*To whom correspondence should be addressed: National Institute of Health Sciences, 1–18–1 Kami-Yoga, Setagaya, Tokyo 158–8501, Japan. Tel.: +81-3-3700-1141; Fax: +81-3-3707-6950; E-mail: fumi@nihs.go.jp

rural regions (Tochigi and Fukushima). The commuter transportation varies depending on the above regions. Therefore, we can imagine that the propagation pattern of influenza could be different accordingly. In Japan, the number of influenza patients in the 04/05 season was twice that in the 03/04 and 05/06 seasons.[16)] It is intriguing to know the influence of the scale of disease (patient number) on the geographical propagation pattern. The problem of which are infected earlier, parents or children, in a society is also taken. Besides the scientific interest, this paper will help the preparedness for national emergencies such as bioterrorism.

MATERIALS AND METHODS

The information about the daily sales amounts of influenza drugs, Tamiflu® capsules and Tamiflu® dry syrup (Chugai Pharmaceutical Co., Ltd., Tokyo, Japan), was offered from pharmacies in Tokyo, Saitama, Kanagawa, Tochigi and Fukushima prefectures. The pharmacy data were available throughout the year, including weekends and holidays. In a few sites, the data from more than one pharmacy are integrated for analysis. For example, in the 04/05 season, two time series are accumulated at site f, three at g and two at i. Consequently, the number of pharmacies is 18, but the number of observation sites is 14.

The mathematical techniques used in this paper which are the cross-correlation function[17)] and lag matrix have already been explained in detail in the previous paper.[15)] A brief explanation is given below for the understanding of this paper.

The cross-correlation function is often used in meteorology, *e.g.*, to measure the time necessary for the rainfall in a mountain to reach a downstream lake. Let the time series of precipitation be $A(t)$ and the time series of the amount of water in a river that flows in the lake be $B(t)$. If the time series of the former has a peak in the time series, $A(t)$, then so will be the latter in $B(t)$. The cross-correlation function is the plot of the correlation coefficients between time series, $A(t+\tau)$ and $B(t)$, as a function of τ:[17)] The time, τ, as the correlation coefficients has its maximum, is referred to as lag. That is, the lag is identified as the time of the strongest correlation between two phenomena.

The lag of influenza infection between two locations can be estimated as mentioned above. The next problem is to find a disease propagation route among many observation sites. Say 14 pharmacies. In this case, the number of lags is too large ($= 91 = {}_{14}C_2$) to be considered simultaneously for the purpose. Our previous paper gave an answer to this problem.[15)] A time series of a pharmacy can have the lags between this pharmacy and all the other pharmacies. The average over the lags, including the lag between the fixed pharmacy and itself (lag = 0), means the relative lag of the pharmacy in question. The difference between the averaged lags of distant pharmacies is proven to be equal to the actual lag between the pharmacies. Using the averaged lags, we can calculate the order of infection period among the pharmacies. A more practical explanation is give in the following section.

RESULTS

The influenza propagation patterns to be estimated below are based on the mathematical techniques, cross-correlation function and lag matrix, shown in Fig. 1 and Table 1, respectively. The former provides the time lag between individual observation sites, and the latter the relative infection periods of the sites. This section takes the above subjects. The disease propagation route is considered in the subsequent section with close reference to the railroad facilities.

Figures 1A and 1B show the time series of the sales amount of Tamiflu® capsules at pharmacies, respectively, h and e in the 04/05 season (for location, also see h and e in Fig. 2). The sales peak of pharmacy h looks twice that of e in height and area. This difference is attributable to the business scales of the pharmacies.

Pharmacies h and e are about 32 km away. The influenza infection in the distant spots cannot synchronize, if the influenza propagates at a limited speed in the area. Therefore, the time period of the sales peak will shift from pharmacy to pharmacy.

The cross-correlation function is helpful to know the time shift of infection between the distant areas.[15)] Figure 1C shows the cross-correlation function of the time series $A(t)$ and $B(t)$, respectively shown in Fig. 1A and 1B. The cross-correlation function (C) has the maximum when $\tau = +8$ days. From the result that the lag is +8 days, we can safely say that the influenza infection around pharmacy e (Fig. 1B) lags 8 days behind h (Fig. 1A).

The correlation coefficient when $\tau = +8$ days is high enough (*ca.* 0.7, see Fig. 1C) to indicate the

Table 1. Individual Lags, M_{ij}, and Averaged Lags, L_i, of Drug Sales at Pharmacies a–n in Tokyo, Saitama and Kanagawa in 04/05 Season

$A(t)$	$B(t)$														Rank	Lag
	a	b	c	d	e	f	g	h	i	j	k	l	m	n	R_i	L_i
a	0	−7	4	7	7	2	3	−1	−2	5	4	−1	2	4	1.93	6.5
b	7	0	8	20	9	8	6	6	1	9	13	7	11	13	8.43	0.0
c	−4	−8	0	6	4	3	1	−3	−4	1	3	−3	3	2	0.071	8.4
d	−7	−20	−6	0	0	0	0	−21	−18	−21	−16	−23	−19	−3	−11.0	19.4
e	−7	−9	−4	0	0	−3	−2	−8	−7	−5	−3	−5	−7	−4	−4.57	13.0
f	−2	−8	−3	0	3	0	−2	−3	−5	−2	−6	−3	0	−6	−2.64	11.1
g	−3	−6	−1	0	2	2	0	−3	−6	0	1	−1	2	0	−0.93	9.4
h	1	−6	3	21	8	3	3	0	−2	3	5	−1	3	3	3.14	5.3
i	2	−1	4	18	7	5	6	2	0	5	2	4	7	2	4.50	3.9
j	−5	−9	−1	21	5	2	0	−3	−5	0	4	−3	0	4	0.71	7.7
k	−4	−13	−3	16	3	6	−1	−5	−2	−4	0	−4	−2	2	−0.79	9.2
l	1	−7	3	23	5	3	1	1	−4	3	4	0	4	4	2.93	5.5
m	−2	−11	−3	19	7	0	−2	−3	−7	0	2	−4	0	−3	−0.50	8.9
n	−4	−13	−2	3	4	6	0	−3	−2	−4	−2	−4	3	0	−1.29	9.7

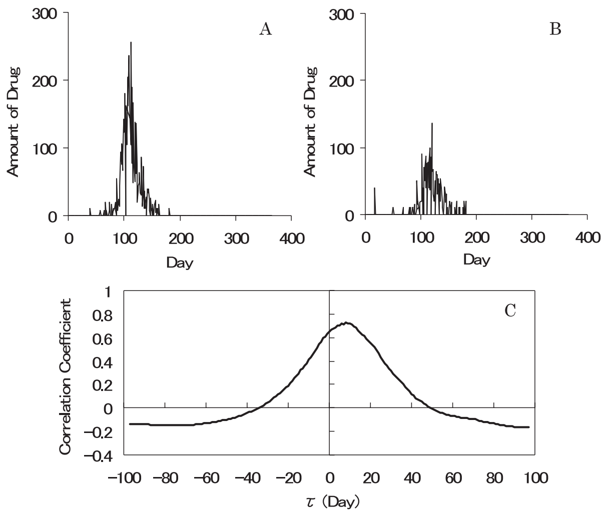


Fig. 1. Daily Variations (A and B) in the Sales of an Influenza Anti-viral Agent (Tamiflu® Capsule) at Pharmacies and Cross-correlation Function (C) of the Variations (A and B) in the 04/05 Season from November 1st, 2004 to October 31st, 2005

(A) pharmacy in site h; (B) pharmacy in site e (for locations, see Fig. 2). The Y-axis denotes the number of capsules dispensed at the pharmacies. The cross-correlation function (C) is smoothed by the moving average method with a window of seven days to eliminate the noise-like fluctuation which comes from a hebdomadal cycle of people's life style in the society.[18)]

strong correlation between the phenomena, $A(t)$ and $B(t)$. However, the high correlation coefficient and finite time lag are only a necessary condition for the infection route from site h to site e.

Table 1 lists the time lags obtained from all the possible $A(t)$ and $B(t)$ of 14 sites a–n in the 04/05 season. The lag matrix, M_{ij}, of Table 1 has 14 rows and 14 columns. The diagonal elements, M_{ii}, are zero, since time series $A(t)$ and $B(t)$ are the same and the correlation coefficient of $A(t+\tau)$ and $B(t)$ is the highest (= 1) when $\tau = 0$. The exchange of the time series in $A(t)$ with the one in $B(t)$ reverses the sign of the lag, *i.e.*, $M_{ij} = -M_{ji}$. Consequently, the lag matrix is an alternating matrix.

The second rightmost column, R_i, of Table 1 lists the average of the time lags in each row, *i.e.*, $R_i = (M_{i1} + M_{i2} + \ldots + M_{i14})/14$ (if i = 1, R_i = 1.93). The mean lag, R_i, can be regarded as the relative time of infection peak. In this paper, the highest value of R_i is defined to be the earliest infection period. In Table 1, R_b (= R_2 = 8.43 days) is the earliest.

The difference between the mean lags, R_i and R_j, is equal to the averaged time lag of infection between sites, i and j. This fact would intuitionally be recognizable and has been proved mathematically.[15)] Let L_i be the difference from the highest mean lag, *i.e.*, in Table 1, $L_i = R_b - R_i$ (R_b = 8.43 days). Hereinafter, L_i is referred to as lag, unless confused with the lag, M_{ij}.

The lags, L_i, listed in Table 1 are mapped in the 04/05 season of Fig. 2. The lag increases with increasing distance from the heart of Tokyo, although only a few exceptions are found. For example, the infection period of site g (Saitama-shi) lags 9.4 days behind site b (Nerima-ku) and site e (Kuki-shi) lags 13.0 days behind site b. The lag between sites e and h is 7.7 days (= $L_e - L_h$ = 13.0 − 5.3) and very close to the lag, M_{he} (= 8 days, see Table 1). The results in the 03/04 and 05/06 seasons are also shown in Fig. 2.

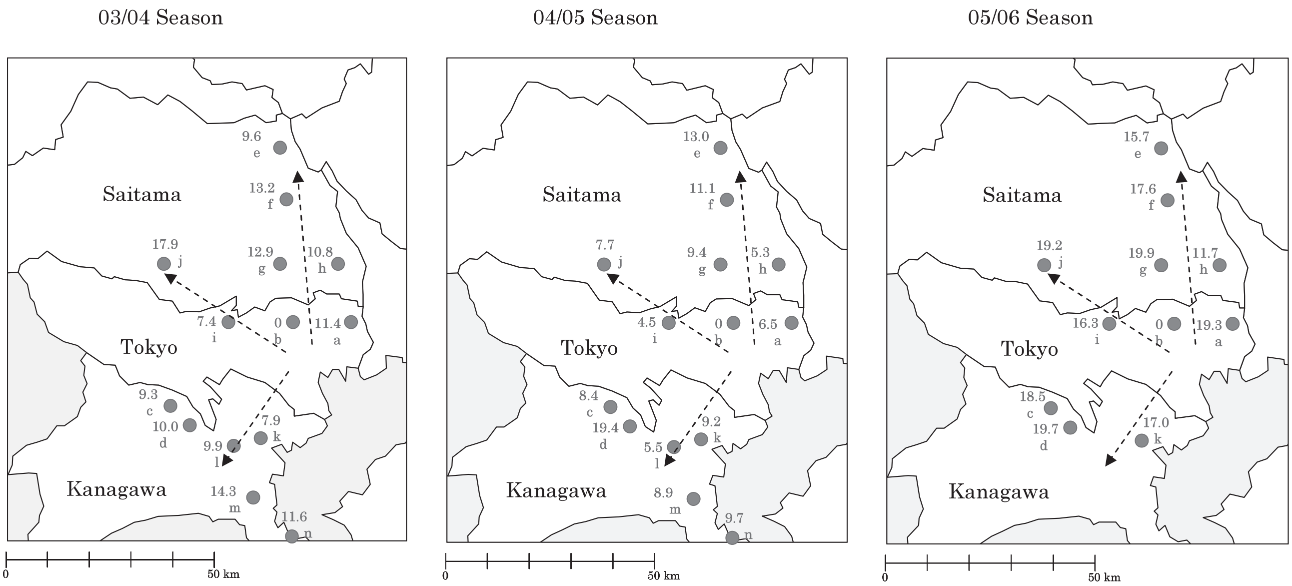


Fig. 2. Influenza Propagation Routes with Time Lags (day) from Pharmacy b in Tokyo and Environs in 03/04, 04/05 and 05/06 Seasons
The sites of pharmacies a–n are marked with circles. The figures near the circles indicate the lags of the sites. The time lags of 04/05 season are listed in the rightmost column (L_i) of Table 1. The propagation routes are indicated by the arrows with broken lines. Pharmacy i is located near an emergency hospital and the other pharmacies are near general clinics (but not emergency ones).

The infection pattern in the wider area is also examined in the 03/04, 04/05 and 05/06 seasons as shown in Fig. 3. The time lags in Tochigi and Fukushima are relative to the earliest infection site, b, of Tokyo. As a whole, the influenza infection seems to be late in Tochigi and Fukushima compared to Tokyo and its vicinity.

Figure 4 illustrates the infection order between adults and children in each observation site. The cross-correlation function is calculated between the time series of Tamiflu® capsules for adults and that of Tamiflu® dry syrup for children at each pharmacy. There seems to be no definite pattern of the infection order, but all the marks (tirangles) of Fig. 4 do not look randomly arranged. We can spot the narrow regions, including several sites, where children are infected earlier and the other narrow regions where adults are earlier.

DISCUSSION

In the region around Tokyo, the railroad systems are stretched in a radial pattern and are intertwined complicatedly to enhance the carrying power. People can easily reach or pass the locations of the pharmacies (● of Fig. 2) from the center of Tokyo through the transport facilities. The people's major movement is either the direction from the center of Tokyo to the suburban areas or reverse direction from the suburbs to the Tokyo downtown.

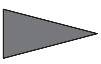
Now, we have the two candidates of the propagation directions: one from Tokyo and the other toward Tokyo. However, taking into account the time lags of the influenza infection in Fig. 2, we can conclude that the influenza spread from the center of Tokyo to Saitama and Kanagawa along the rail lines in the seasons examined here as pointed out by the arrows of Fig. 2.

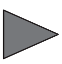
These disease propagation routes cannot uniquely be determined from the pharmacy data. However, the routes estimated here can be considered acceptable, because, for example, the route, b → g → f is probable, but the route, b → i → j → f is improbable (see below).

The Internet Web sites of railway companies enable us to efficiently obtain the information concerning the daily average of passengers who got on a train at almost all the stations. In 2005, Keihin-Tohoku line along the north route (arrow to e) accepted on the average 60000 passengers a day at a station. This average is calculated over nine stations from Akabane to Omiya. However, Omiya station, major relay point, which took on the average 230000 passengers a day is eliminated from the calculation. In the west route (arrow to j), Seibu-Ikebukuro line accepted about 40000 passengers a day on the average of 26 stations from Ikebukuro

Fig. 3. Time Lags of Influenza Infection in Tochigi and Fukushima Prefectures

In Tokyo, Saitama and Kanagawa, ● denotes the location of the pharmacies shown in Fig. 2 and → indicates the infection routes shown in Fig. 2. In Tochigi (north of Saitama) and Fukushima (north of Tochigi) prefectures, the block arrows denote the infection periods, respectively,

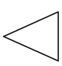
 more than or equal to 20 days;

 less than 20 days and more than or equal to 10 days;

 less than 10 days and more than or equal to 0 day;

later than the infection period in the earliest infection site b of Fig. 2 and

 more than 0 day and less than or equal to 10 days;

 more than 10 days and less than or equal to 20 days;

earlier than the infection period in the earliest infection site b of Fig. 2.

to Hanno and Seibu-Shinjuku line about 50000 a day at each of 17 stations from Shinjuku to Tanashi. On the other hand, Kawagoe line and Hachiko line which connect sites f and j accepted about 6000 passengers a day at each of 11 stations from Omiya to Higashi-Hanno except major relay points, Omiya and Kawagoe (on the average 36000 a day).

The passengers of the railway facilities along the north and west infection routes of Fig. 2 are ten times in number those between sites f to j. The similar trend can be found in the railroad along the south route (arrow to l) and between sites j and l.

The speed of disease propagation is defined as the distance between two sites, i and j, divided by the time lag, $|L_i - L_j|$.[15] The propagation speed within the infection routes in the 04/05 season from pharmacy b to another can be estimated: a, 2.2; c, 4.2; d, 1.8; e, 3.2; f, 2.7; g, 1.5; h, 3.4; i, 3.5; j, 4.5; k, 3.1; l, 6.0; m, 4.8; n, 5.3 km/day. The average is 3.2 km/day. The ratio of the highest to the lowest speed (= 6.0/1.8 = 3.3) is so small that it corroborates the reliability of our estimation (see below).

The between-route propagation speed is totally different from the within-route speed (= 3.2 km/day in the 04/05 season). For example, the propagation speed between pharmacies f and j is 9.9 km/day and that between j and l is 21.3 km/day.

Noticing the above discussion about the number of passengers at stations and the propagation speeds within and between the infection routes, we can conclude that in the 04/05 season, influenza appears to have propagated through the infection routes shown in Fig. 2 and not between the routes.

In our previous paper,[15] the data were collected from 14 pharmacies (10 observation sites), whereas this paper treats the data from 18 pharmacies (14 sites, ● in Fig. 2). Sites, d, l, m and n, are newly analyzed in this paper. It is interesting that the within-route propagation speed (3.5 km/day) in the previous paper[15] is similar to the speed (3.2 km/day) in

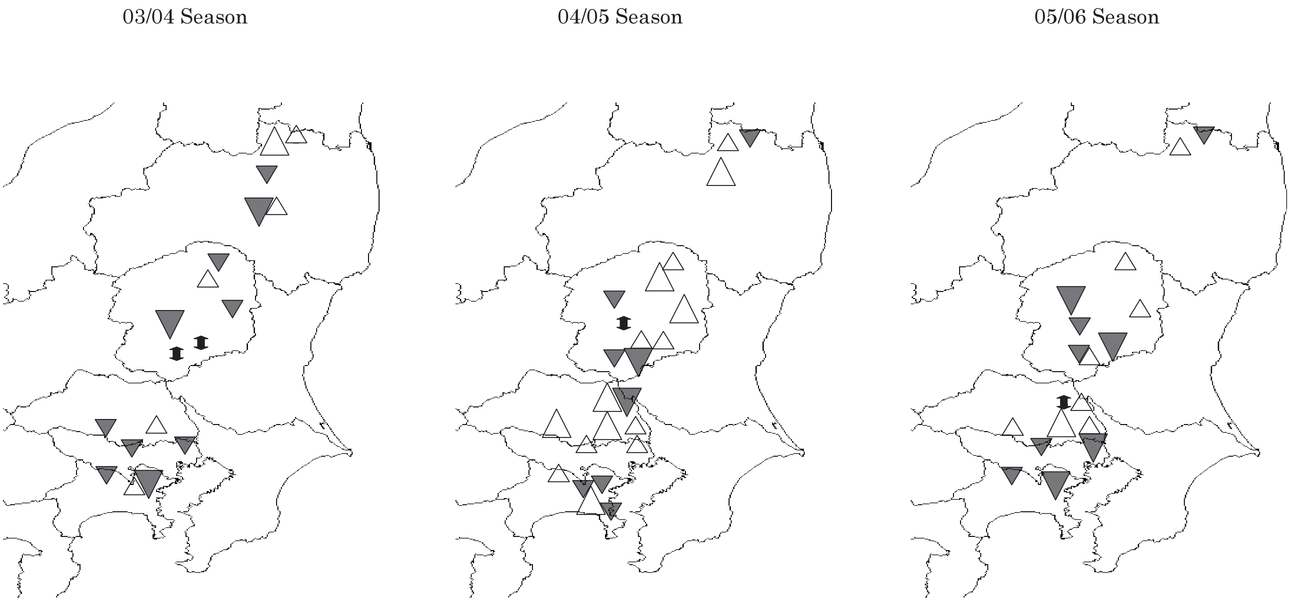


Fig. 4. The Infection Order of Adults and Children in Tokyo and Its Neighborhood Including Saitama, Kanagawa Tochigi and Fukushima Prefectures

The block arrows denote the infection periods, respectively,

 more than or equal to 6 days;

 less than 6 days;

earlier for adults than children,

 more than or equal to 6 days;

 less than 6 days;

earlier for children than adults, and

 simultaneously infected for adults and children.

this paper in spite of the different observation sites.

In the 03/04 season, the similar results are obtained. The time lags and infection routes estimated are shown in Fig. 2. A single infection focus can also be indicated near pharmacy b. The propagation speed within the infection routes in the 03/04 from pharmacy b can be estimated: a, 1.2; c, 3.9; d, 3.5; e, 4.4; f, 2.2; g, 1.1; h, 1.7; i, 2.1; j, 1.9; k, 3.7; l, 3.3; m, 3.0; n, 4.4 km/day. The average is 2.8 km/day. The speed between the routes is much different from the within-route average. The speed between f and j is 7.1 km/day and that between j and l is 5.9 km/day.

The average propagation speed in the 04/05 season (3.2 km/day) is estimated to be slightly higher than in the 03/04 season (2.8 km/day). The significance of the difference is statistically examined by the t-test. The within-route speeds at each pharmacy are compared between the 03/04 and 04/05 seasons in the t-test. For example, at site a, the difference is −1.0 km/day (= 1.2 − 2.2). On the other hand, the between-route speeds are different from each other and excluded from the test. The null hypothesis that the difference in speed between the seasons over all the pharmacy sites except site b is distinguishable from zero is denied with 5% significant level.

The number of influenza patients found in Japan in the 04/05 season is approximately twice that in 03/04 season.[16] The influenza drugs in pharmacy i were sold in the 04/05 season twice in the 03/04 season. In both the seasons, however, the averaged passengers a day at a railway station were comparable, and the infection routes and speeds within the route are estimated to be almost identical. The comparable propagation speeds may be due to the definition, but have yet to be elucidated in future study.

In the 05/06 season, we can conclude the same propagation pattern (see Fig. 2). The influenza seems to have had the same routes, but the averaged propagation speed (= 1.5 km/day) is a half of the averages in the 03/04 and 04/05 seasons. The propagation speed within the infection routes in the 05/06 season from pharmacy b can be estimated: a, 0.7; c, 1.9; d, 1.8; e, 2.7; f, 1.7; g, 0.71; h, 1.5; i, 0.96; j, 1.7; k, 1.7 km/day. This slow propagation is attributable to the relatively earlier infection periods of site b.

The south region of Tochigi prefecture can be reached through several railways from Tokyo, *e.g.*, Utsunomiya line and Keihin Tohoku line. The city in the middle of Tochigi (Nikko) is within the reach of Tobu Nikko line. The eastern region of Tochigi and marked sites of Fukushima prefecture can be made it to through Tohoku Hon Line. As far as the 04/05 season in Fig. 3 is concerned, the infection seems to have spread in the route along the above mentioned railways: Tokyo → Saitama → Tochigi → Fukushima. In fact, while the lag in site e (see Fig. 2) is 13 days, the lags in the southern region of Tochigi are slightly longer than that, ranging from 10 to 20 days in most cases (see Fig. 3). The two pharmacies in the middle of Fukushima have much longer lags, *i.e.*, more than 20 days. However, the earlier infection than Tokyo is observed in several sites of the southern region of Tochigi in the 03/04 season, and therefore, the propagation route in the 04/05 season does not necessarily apply to the other seasons.

In conclusion, although the available information was limited to only a few dozens of community pharmacies, we can demonstrate the routes and speeds of influenza propagation in Tokyo and nearby prefectures in three seasons from 2003 to 2006. However, a variety of things remain to be solved in the future work of health vigilance. The other anti-influenza drugs such as amantadine and zanamivir need also be examined for more comprehensive understanding of the geographical propagation pattern of influenza.

In Figs. 3 and 4, the pharmacy locations run toward the north from the vicinity of Tokyo. This is because of the voluntary participation of the pharmacies in this work. We would have analyzed the data from other prefectures around Tokyo such as Chiba, Yamanashi, Ibaraki and Gunma, but the present study could not enjoy the participation. Widespread observation sites will be required for detailed study.

We believe that this paper paves the way for the vigilance of people's health based on the information from pharmacies and drug stores.

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