YAKUGAKU ZASSHI 126(4) 311—314 (2006) © 2006 The Pharmaceutical Society of Japan

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A Method for Estimating the Order of Influenza Infection between Adults and Children

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(Received December 9, 2005; Accepted February 3, 2006; Published online February 6, 2006)

This paper puts forward a method for determining the infection order of influenza between adults and children from the daily variations in the amount of influenza anti-viral agents treated at a pharmacy. The time series of Tamiflu Capsule for adults and Tamiflu Dry Syrup for children are compared by means of the cross-correlation function. The results from pharmacies located in Tokyo and Kanagawa show that the influenza infection period of adults is earlier than that of children, indicating the infection order: first adults and second children. However, a pharmacy in Saitama yields no clear result.

Key words——correlation; pharmacy; influenza; spectral analysis

INTRODUCTION

The mathematical techniques of spectral analysis have been introduced in the fields of medical and pharmaceutical sciences to analyze the time variations in the infection of a disease such as measles and influenza.[1—8] Among the typical mathematical techniques are the auto-correlation function, cross-correlation function, power spectrum, maximum entropy method and moving-average method.[9]

A recent paper[10] used the cross-correlation function between time variations in drug prescriptions at distant pharmacies to estimate the infection route and speed of influenza in Tokyo and its vicinity. The in-depth discussion of the infection pattern from the medical and social viewpoints has yet to be made in the future work. However, the above paper is the first attempt to make an extensive vigilance of people's health on the basis of the information network among pharmacies and drugstores. Hereinafter, this study is referred to as health vigilance.

The present paper demonstrates another way to use the cross-correlation function in health vigilance. Now, it is a good opportunity to clarify the definition and applicability of the function. In general, the cross-correlation function between time series, $A(t)$ and $B(t)$, is defined as:[9]

$$R(\tau)=\frac{E[A(t)B(t+\tau)]}{\sqrt{E[A(t)^2]E[B(t)^2]}} \qquad (1)$$

where $E[.]$ denotes the mean over time, t, of the random variables inside the square brackets and τ is called lag. The numerator of the right side of Eq. (1) denotes the covariance of random variables, $A(t)$ and $B(t+\tau)$, and the denominator is the product of the standard deviations (SDs) of $A(t)$ and $B(t)$. The means of $A(t)$ and $B(t)$ are assumed to be zero, respectively. $R(\tau)$ describes the correlation coefficients between $A(t)$ and $B(t+\tau)$ as a function of τ. If $A(t)=B(t)$, Eq. (1) represents the auto-correlation function.

The following types of the cross-correlation functions are defined in this series of study:

site correlation function in which $A(t)$ and $B(t)$ are the time variations in a formulation at different pharmacies (sites);

drug correlation function in which $A(t)$ and $B(t)$ denote the time variations in different formulations supplied at a pharmacy.

The previous paper[10] adopted the site correlation function, but the approach of this paper is based on the drug correlation function. The latter gives an answer to the interesting problem of which are earlier infected with influenza in a limited area, adults or children. The aim of this paper is the proposition of the new method itself, and the resulting order of the influenza infection is not discussed in detail in many respects.

The nation-wide surveillance of influenza patients diagnosed at hospitals and clinics in Japan are open to the public in Infectious Diseases Surveillance Center and ML Influenza Ryukou Zensen Jouhou DB. However, the site and drug correlation functions have

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not been used by the surveillance.

METHODS

The information about the prescriptions of influenza drugs was collected from the pharmacies in and around Tokyo: Homecare Pharmacy Hanno, 21–5 Shinmachi, Hanno, Saitama; Tanashi Honcho Pharmacy, 4–25–5 Tanashi, Nishi-Tokyo, Tokyo; Homecare Pharmacy Yokohama, 1268–103 Shinohara, Kohoku, Yokohama, Kanagawa. The pharmacies were open throughout the year and the data of weekends were also available. The pharmacy in Nishi-Tokyo is located near an emergency hospital, and the other pharmacies are near clinics (but not emergency ones).

RESULTS AND DISCUSSION

Figure 1 shows the time series of the amount of influenza anti-viral agents supplied daily for adults and children at the pharmacies. The drug is Tamiflu Capsule 75 (Chugai Pharmaceutical Co., Ltd.) for adults and Tamiflu Dry Syrup 3% (Chugai Pharmaceutical Co., Ltd.) for children. The Y-axis denotes the total number of capsules (A, B and C) and the total weight of syrup (A′, B′ and C′). These data were collected at three pharmacies in the Kanto area: Yokohama (A and A′); Nishi-Tokyo (B and B′); Hanno (C and C′).

The influenza had been prevalent at the districts till the middle of March in 2004 so that the anti-viral agents were frequently supplied over the period. The strong frequency with the period of seven days appears in Fig. 1. This hebdomadal cycle of prescriptions results from the concentrated prescriptions on Sundays and Mondays and can be related to the characteristics of infection and the life style of people in the cities.[8] That is, the infection chances of patients at workplaces, elementary schools and kindergartens will be more during week days. The drugs are recommended to be administered to the patients

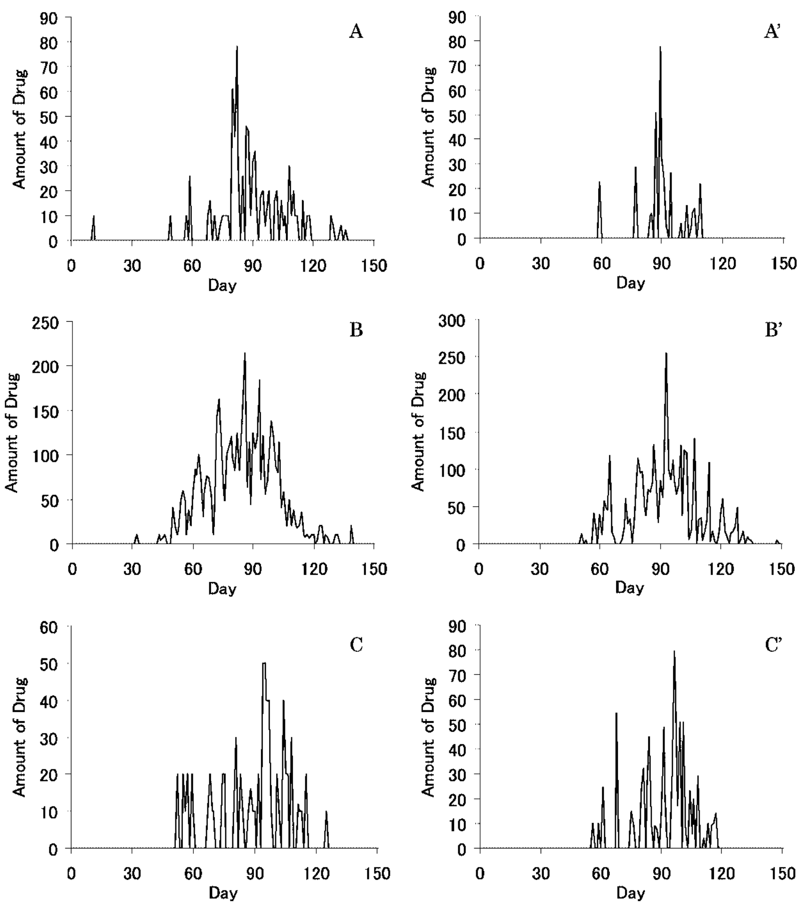

Fig. 1. Time Series of Influenza Drug Prescriptions for Adults (Left) and Children (Right) since November 1st in 2003 (150 days)

A, B and C: Tamiflu Capsule (Y axis: capsules). A′, B′ and C′: Tamiflu Dry Syrup 3% (Y axis: gram). Pharmacies located in: (A and A′) Yokohama, (B and B′) Nishi-Tokyo, (C and C′) Hanno.

within two days after the onset of symptoms. These facts may be the reason why the influenza prescriptions have a tendency to converge on Sundays and Mondays.

Figure 2 shows the drug correlation functions between the time series of the prescriptions for the adults and children at the pharmacies located in Yokohama (A), Nishi-Tokyo (B) and Hanno (C). Figure 2(A) is the cross-correlation function between Figs. 1(A) and 1(A′), Fig. 2(B) is that between Figs. 1(B) and 1(B′) and Fig. 2(C) is that between Figs. 1(C) and 1(C′).

Figures 2(A) and 2(B) both show the maximum correlation when $\tau=7$ days. This result indicates that as for the influenza prescriptions, the children lag seven days behind the adults in Yokohama and Nishi-Tokyo.

The above infection pattern is probable. The action of children is usually restricted within a narrow region around their homes and schools, but the action radius of adults is longer than that of children. Therefore, the adults have more chances to catch the disease. Consequently, the adults are first infected by influenza and second, the children contract it by infection.

In Fig. 2(C), however, no conspicuous time lag can be found at the maximum correlation. The following reasons for the difference from Figs. 2(A) and 2(B) can be thought of. First, the sample size of the pharmacy in Hanno (Fig. 2(C)) will be too small for spectral analysis (compare the Y-axes of Fig. 2). Second, the action radius of the adults in Hanno will not be so long as in Yokohama and Nishi-Tokyo possibly due to the occupations of the adults. The second reason poses an interesting problem of social science, but now it is open, because the private information of patients cannot be disclosed.

The population statistics as of January 1, 2005 tells that people of greater than or equal to 65 years old, people of less than 65 years old and greater than or equal to 15 years old, and people of less than 15 years old (population) are 13, 74 and 13% (301616) for Kohoku; 18, 69 and 13% (185140) for Nishi-Tokyo; 18, 68 and 14% (84982) for Hanno, respectively. The people of less than 10 years old are 8.9% for Kohoku, 8.7% for Nishi-Tokyo and 8.2% for Hanno. Hanno has a small population and small ratio of people of less than 10 years old compared to Kohoku (Yokohama) and Nishi-Tokyo. However, the relationship between the above fact and result of Fig. 2 is not clear.

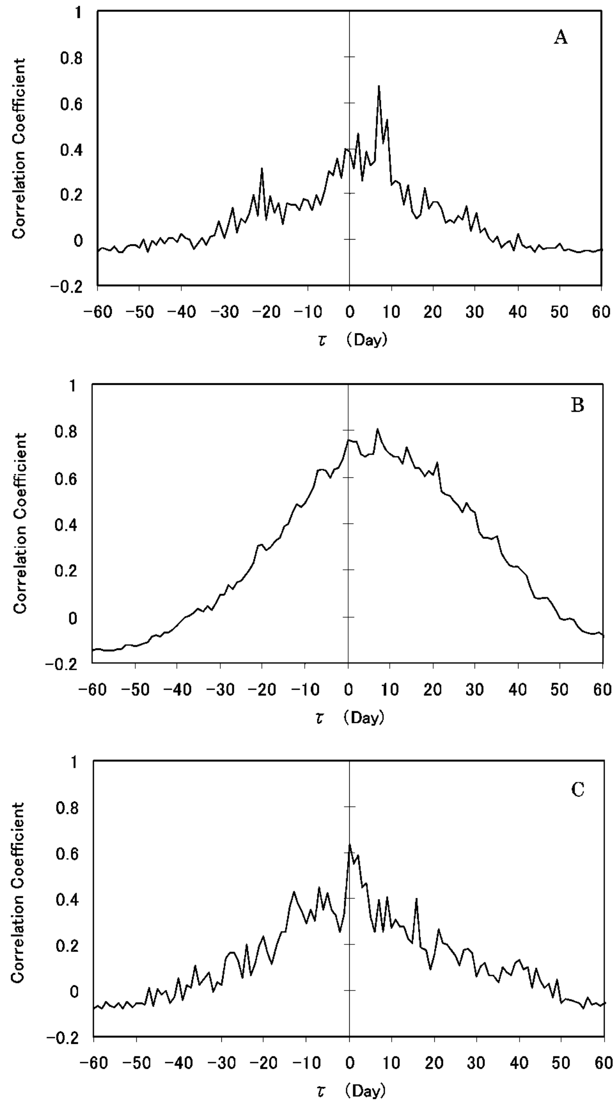

Fig. 2. Cross-correlation Functions between Influenza Drug Prescriptions for Adults and Children at Pharmacies Located in Yokohama (A), Nishi-Tokyo (B) and Hanno (C)
Drug: Tamiflu capsule for adults and Tamiflu Dry Syrup 3% for children. The data of 365 days since November 1st in 2003 are analyzed.

The hebdomadal cycle appearing in the time series could obscure the determination of the maximum correlation time in Fig. 2. The moving average method of 7 days was performed for the drug correlation functions of Fig. 2 and the maximum correlation was spotted at 6 days for Yokohama (A), 4 days for Nishi-Tokyo (B) and 2 days for Hanno (C) (data not shown). These results from the smoothing are near those from the original data and the above discussion can be considered valid. As is well-known, there are the merits and demerits of the smoothing and the above discussion is based on the data without smoothing.

The time lags of the drug correlation functions have been interpreted based on the actions radii of adults and children. However, the causes are multifactorial and the above interpretation is too simple. For example, the following explanation is also feasible. Adults can consult a doctor of their own accord. As for infants, however, the timing of the medical consultation which depends totally on the observation by their parents can be delayed. Etiological consideration, especially from a virological perspective, e.g., incubation period and disease carriers, is necessary for future study.

The spatial understanding of disease propagation has been done for decades,[11,12] and the surveillance of the influenza infection has started in Japan.[13—15] The study of the health vigilance, including the results of this paper, will be a great help to cope with the pandemic problems of influenza.

The drug correlation function and site correlation function, defined in the introductory section, have the distinctive meanings, although they are the same mathematical formalism. They will be available for many purposes in health vigilance.

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