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# Time-Series Analysis of Coxsackievirus B Serotype Surveillance Data in Japan

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Objective: Coxsackievirus B (CVB) is associated with the development of human diseases including type 1 diabetes. Previous studies identified cyclical variations in type 1 diabetes incidence—peak incidences occurring in 4- to 6-year periods in two regions in England, a 5-year period in Western Australia, and 5.33-year period in Poland. However, it is not clear whether CVB infection rates demonstrate similar cyclical variation characteristics. The purpose of this study was to characterize the periodicity in CVB surveillance data.

Results: Maximum entropy spectral analysis was performed on monthly CVB surveillance data in Japan. In addition to demonstrate a 1-year cycle for all the serotypes, spectral peaks were demonstrated for dominant cycles—6.9-, 3.8-, 4.3-, 9.5-, and 7.8- year periods for CVB1, CVB2, CVB3, CVB4, and CVB5, respectively. Pearson correlation was used to compare the least-squares fit curves based on periods estimated from the analysis with the original data. The results for all five serotypes—CVB1, CVB2, CVB3, CVB4, and CVB5—demonstrated good correlation— $\rho = 0.96$, $\rho = 0.60$, $\rho = 0.90$, $\rho = 0.88$, and $\rho = 0.67$, respectively. This method could be a useful tool for the efficient investigation of CVB as a pathogen of type 1 diabetes.

Keywords: Type 1 diabetes; Coxsackievirus B; time-series analysis; periodicity; surveillance; Japan

## INTRODUCTION

Coxsackievirus B (CVB) have recently attracted attention as a cause of type 1 diabetes, which has a high incidence among children in European countries [1,2]. The estimated increase in annual incidence of type 1 diabetes in Europe was 3.9% (95% CI 3.6%, 4.2%) from 1989 to 2003; worldwide, the estimated annual increase was 2.8% (95% CI 2.4%, 3.2%) from 1990 to 1999 [3].

Examining the periodic structure of CVB serotype surveillance data is essential for predicting the epidemic of type 1 diabetes. Some researchers have reported cyclical variations in yearly incidence rates of type 1 diabetes—4-year intervals in the Yorkshire region in England from 1978 to 1990 [4], a 6-year cyclical pattern in a neighboring area of northeast England from 1990 to 2007 [5], a sinusoidal cycle with peaks every 5 years in Western Australia from 1985 to 2010 [6], and a 5.33-year periodicity in Poland during the period 1989-2012 [7]. More recently, to help clarify recent trends in European incidence rates, European Diabetes registry data were analyzed from over 84,000 children in 26 European centers representing 22 countries from 1989 to 2013, with separate estimates of incidence rate increases derived in five subperiods [3].

To date, no studies have clarified whether surveillance data for CVB serotypes show similar cycles as those in type 1 diabetes incidence data, likely because studies investigating publicly available CVB serotype surveillance data for Europe are lacking. On the other hand, in Japan, CVB serotype surveillance data have been collected for 20 years [8]. The purpose of this study was to investigate the periodic structure of Japanese CVB serotype surveillance data by using time-series analysis based on the maximum entropy method (MEM) in the frequency domain and the least squares method (LSM) in the time domain [9, 10].

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## Material and Method

### CVB Serotype Surveillance

Monthly surveillance data of CVB serotypes (CVB1, CVB2, CVB3, CVB4, and CVB5) from January 2000 to December 2018 (228 data points) were analyzed. The number of specimens that were tested positive for pathogens and viruses, including CVB serotypes, are regularly reported to the National Institute of Infectious Disease Surveillance Center (Tokyo, Japan). These data are published in the monthly periodical *Infectious Agents Surveillance Report* [11].

### MEM spectral analysis

Power spectral density (PSD) based on maximum entropy method (MEM), $P(f)$ (where $f$ represents frequency), for the time series with equal sampling interval $\Delta t$, can be expressed by

$$P(f) = \frac{P_m \Delta t}{\left| 1 + \sum_{k=-m}^{m} \gamma_{m.k} \exp\left[-i 2\pi f k \Delta t\right] \right|^2}, \qquad [1]$$

where the value of $P_m$ is the output power of a prediction-error filter of order $m$ and $\gamma_{m,k}$ is the corresponding filter order. The value of the MEM-estimated period of the $n$-th peak component $T_n$ (=1/$f_n$; where $f_n$ is the frequency of the $n$-th peak component) can be determined by the positions of the peaks in the MEM-PSD.

### Least squares method (LSM)

The validity of the MEM spectral analysis results was confirmed by calculation of the least squares fitting (LSF) curve to the original time series with MEM estimated periods. The formulation of the LSF curve in $X(t)$ is described as follows:

$$X(t) = A_0 + \sum_{n=1}^{N} A_n \cos\left\{2\pi f_n (t + \theta_n)\right\}, \qquad [2]$$

which is calculated using the LSM for $x(t)$ with unknown parameters $f_n$, $A_0$ and $A_n$ ($n$ = 1, 2, 3,⋯, $N$), where $f_n$ (=1/$T_n$; $T_n$ is the period) is the frequency of the $n$-th component, $A_0$ is a constant that indicates the average value of the time series data, $A_n$ and $\theta_n$ are the amplitude and the phase of the $n$-th component, respectively, and $N$ is the total number of components.

## Results

### MEM Spectral Analysis of the Surveillance Data

Monthly surveillance data of CVB serotype from January 2000 to December 2018 are shown in Figure 1. Therein, all incidence data show a yearly cycle with large epidemics every few years, for example, CVB1 (Figure 1a) in 2004 and 2011, and CVB2 (Figure 1c) in 2005 and 2009.

### Periodicity of the Surveillance Data

Figure 2 shows power spectral densities (PSDs) obtained with the MEM spectral analysis (Equation [1]) for the data in Figure 1. In each plot— CVB1 (Figure 2a), CVB2 (Figure 2b), CVB3 (Figure 2c), CVB4 (Figure 2d), and CVB5 (Figure 2e)—prominent spectral peaks were observed at $f$ = 1.0 [units (1/year)], corresponding to the 1-year cycle, that is, the seasonal cycle. In the low-frequency range, $f$ < 1.0, reflecting oscillations longer than the 1-year cycle, several prominent spectral peaks were observed. In each power spectral density plot, the dominant spectral peak was observed during an approximately 3- to 5-year period. For each serotype, five dominant spectral frequency mode peaks with corresponding periods and powers were identified, and listed in Table 1.

With the five periodic modes that were clearly observed in each PSD (Table 1), the least squares fitting (LSF) curve (Equation [2]) for each serotype was calculated. Each LSF curve thus obtained is presented in Figure 1.

Each LSF curve reproduced the original data well (Figure 1), which confirmed that the periods from MEM spectral analysis (Figure 2, Table 1) were accurate. Pearson correlations between the original data and the LSF curves— $\rho$ = 0.96, $\rho$ = 0.60, $\rho$ = 0.90, $\rho$ = 0.88, and $\rho$ = 0.67 for CVB1, CVB2, CVB3, CVB4 and CVB5, respectively—further demonstrated a good fit.

## Discussion and Conclusions

An important finding of this study was the identification of 3- to 5-year period for the epidemic of enterovirus in the surveillance data in Japan (Figure 2 and Table 1). This period is similar to that observed in time-series data on the number of patients with type 1 diabetes in Europe [2]. Therefore, if periodicities in CVB infection rates similar to those identified in these surveillance data in Japan is found in also European data, the association between CVB serotypes and type 1 diabetes would be supported. Coun-

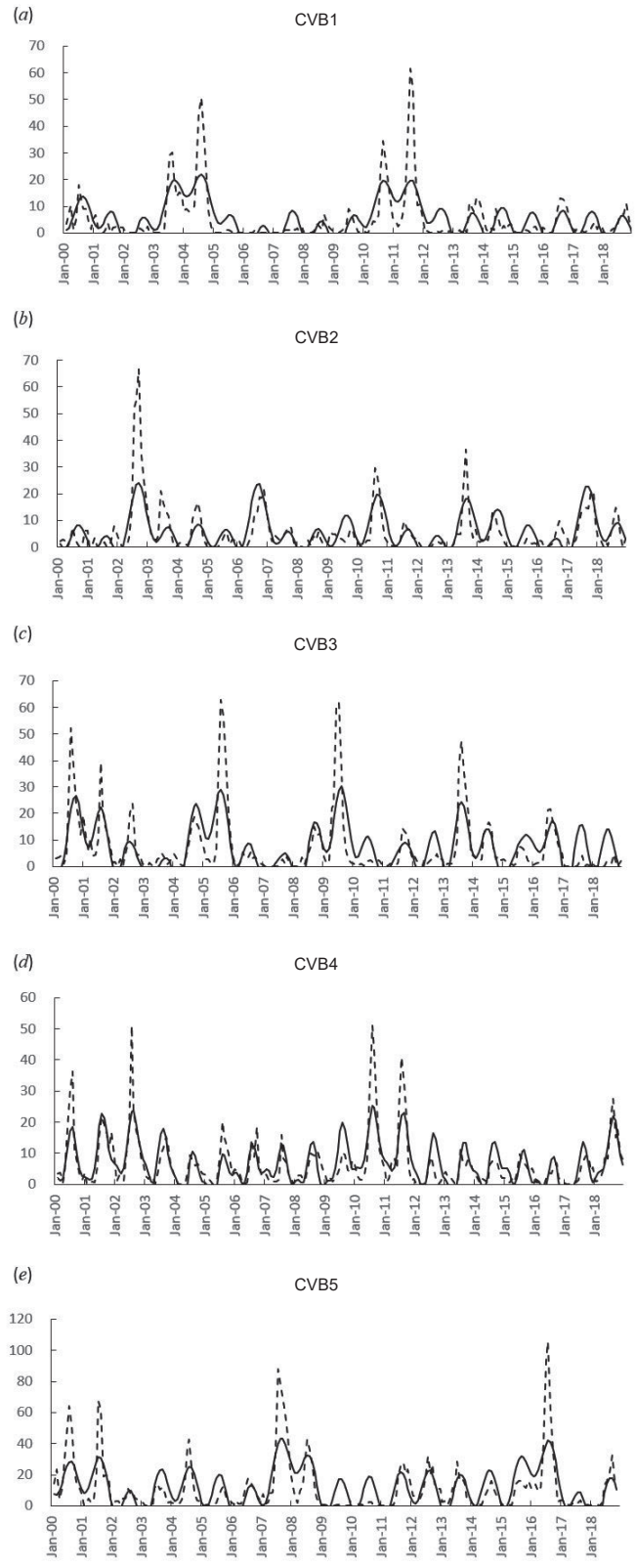


Fig 1 Comparison of the least-squares fitting curves calculated for long-term trends (solid line) with original data (dotted line) for (a) CVB1, (b) CVB2, (c) CVB3, (d) CVB4, and (e) CVB5.

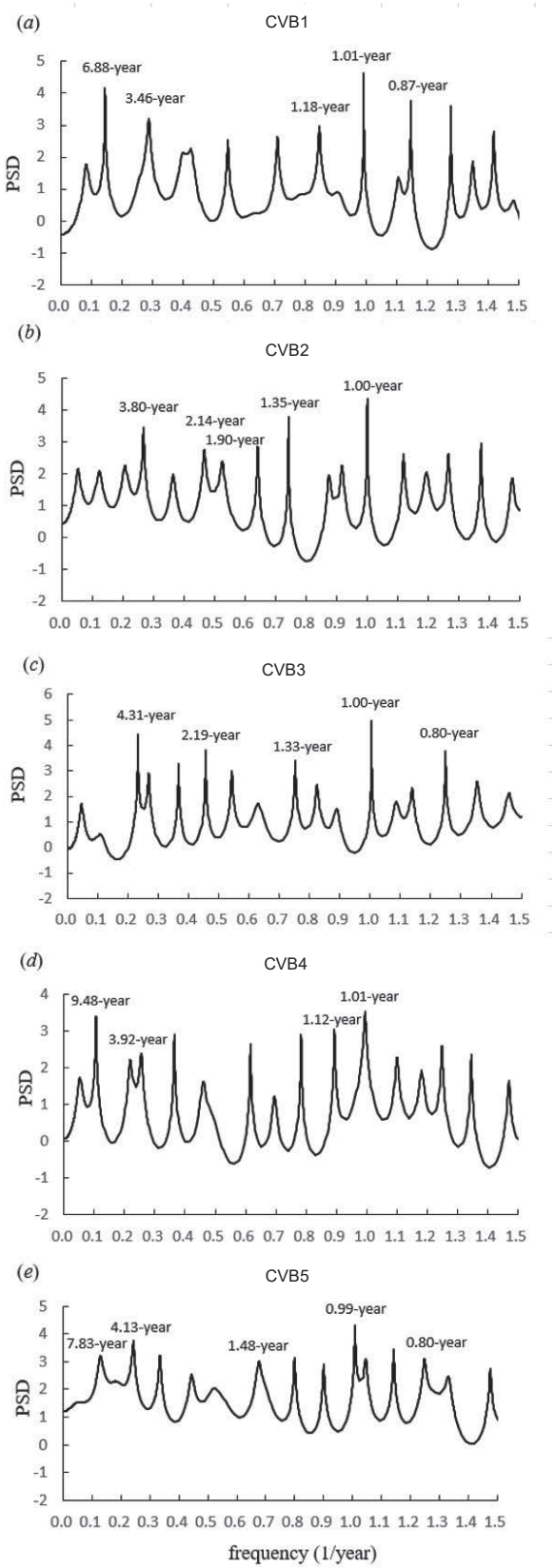


Fig 2 Power spectral density plots of the original data for (a) CVB1, (b) CVB2, (c) CVB3, (d) CVB4, and (e) CVB5.

Table 1. Characteristics of the five dominant spectral peaks shown in Figure 2.

| | Frequency (1/year) | Period (year) | Power |
|---|---|---|---|
| CVB1 | 0.15 | 6.88 | 18.52 |
| | 0.29 | 3.46 | 15.07 |
| | 0.85 | 1.18 | 1.18 |
| | 0.99 | 1.01 | 16.10 |
| | 1.15 | 0.87 | 6.61 |
| CVB2 | 0.26 | 3.80 | 12.97 |
| | 0.47 | 2.14 | 5.85 |
| | 0.53 | 1.90 | 4.17 |
| | 0.74 | 1.35 | 4.42 |
| | 1.00 | 1.00 | 14.32 |
| CVB3 | 0.23 | 4.31 | 25.63 |
| | 0.46 | 2.19 | 9.2 |
| | 0.75 | 1.33 | 7.74 |
| | 1.01 | 1.00 | 32.28 |
| | 1.25 | 0.80 | 10.31 |
| CVB4 | 0.11 | 9.48 | 6.93 |
| | 0.26 | 3.92 | 2.69 |
| | 0.89 | 1.12 | 3.73 |
| | 1.00 | 1.01 | 25.26 |
| | 1.98 | 0.50 | 5.35 |
| CVB5 | 0.13 | 7.83 | 32.09 |
| | 0.24 | 4.13 | 46.68 |
| | 0.68 | 1.48 | 19.78 |
| | 1.01 | 0.99 | 53.25 |
| | 1.25 | 0.80 | 18.79 |

tries with large numbers of patients with type 1 diabetes, such as Finland, have published surveillance data for enteroviruses but not for serotype-specific enterovirus. To resolve the high incidence of type 1 diabetes in Europe, access to serotype-specific enterovirus surveillance data is essential. We anticipate that this method of time-series analysis will be a useful tool for elucidating periodicity in serotype-specific enterovirus surveillance data.

## Limitation

A limitation of this study was that a direct comparison between CVB infection rate and type 1 diabetes periodicities could not be performed since we did not have access to CVB epidemiological time-series data for European countries. Investigating the correlation of CVB infection rates with type 1 diabetes, for example in countries such as Finland, would allow efficient estimation of CVB as pathogen of type 1 diabetes, to contribute to reducing the incidence of type 1 diabetes.

## List of abbreviations

LSF, least squares fitting; MEM, maximum entropy method; PSD, power spectral density.

## Declarations

### Ethics approval and consent to participate

Not applicable

### Consent for publication

Not applicable.

### Availability of data and material

The dataset of surveillance data analyzed during the current study are available from ref. [9].

### Competing interests

We declare that I have no competing interests.

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