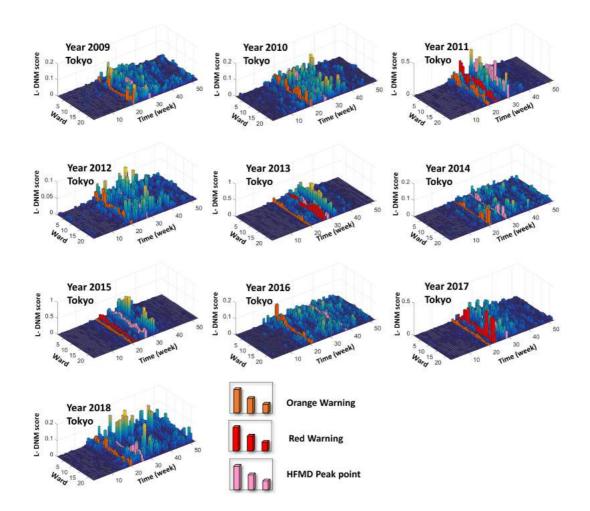
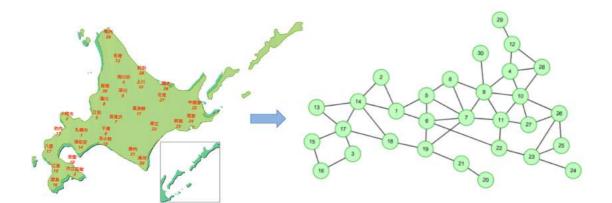
## Supplementary Information of Identifying Pre-outbreak Signals of Hand, Foot and Mouth Disease Based on Landscape Dynamic Network Marker

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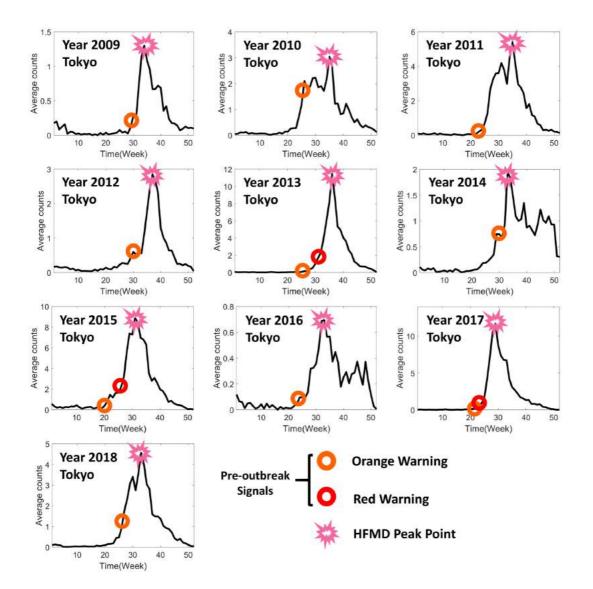


**Supplementary Figures** 

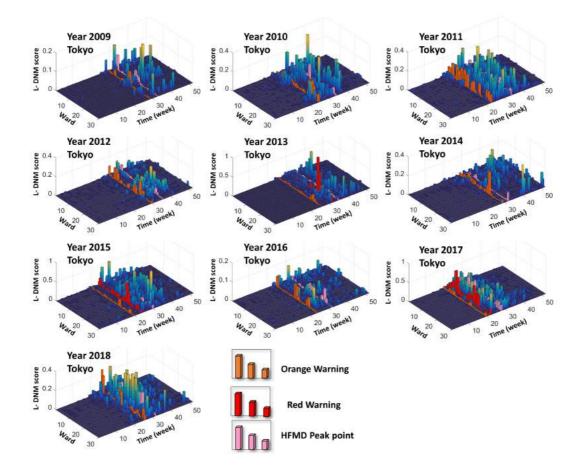
Figure S1: The landscape of L-DNM scores for 23 wards in Tokyo between the years 2009 and 2018. The orange column point to the first appearance of warning signals, the red column indicates that the scale of infection is expanding and the pink column indicates an outbreak. Obviously, the warning signals are sensitive and effective.



**Figure S2: The city network for Hokkaido region.** Based on the geographic distribution of 30 districts and their adjacent relationship, a 30-node network model is constructed for analysis.



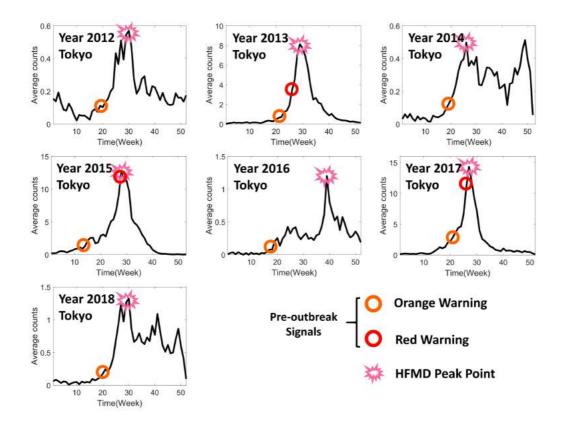
**Figure S3: Forecast of seasonal HFMD outbreaks in Hokkaido between the years 2009 and 2018.** In each figure, the y-axis is the average number of patients in each clinic; the x-axis represents the period from the first week of the year to the last week of the year. Besides, the markers of different colors and shapes markers are used to identify warning signals or outbreak points. Clearly, when the actual number of clinic visits has not increased significantly, significant changes in L-DNM scores have been detected, indicating the presence of pre-outbreak signals.



**Figure S4: The landscape of L-DNM score for 30 wards in Hokkaido between the years 2009 and 2018.** In each landscape figure, the L-DNM scores of 30 wards in Hokkaido are presented annually. The orange column point to the first appearance of warning signals, the red column indicates that the scale of infection is expanding and the pink column indicates an outbreak. Clearly, the warning signals are earlier than the outbreaks.



**Figure S5: The network for Osaka, Japan.** Based on the geographic distribution of 11 districts and their adjacent relationship, a 11-node network model is constructed for analysis.



**Figure S6: Forecast of seasonal HFMD outbreaks in Osaka between the years 2012 and 2018.** In each figure, the y-axis is the average number of patients in each clinic; the x-axis represents the period from the first week of the year to the last week of the year. Besides, the markers of different colors and shapes are used to identify warning signals or outbreak points. Seven HFMD outbreaks occurred in Osaka from year 2012 to 2018, among which L-DNM method provided pre-outbreak signals for five outbreaks accurately.