Original Article

Using Interrupted Time Series Design to Analyze Changes in Hand, Foot, and Mouth Disease Incidence during the Declining Incidence Periods of 2008-2010 in China

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Abstract

Objective To identify patterns of hand, foot and mouth disease (HFMD) incidence in China during declining incidence periods of 2008, 2009, and 2010.

Methods Reported HFMD cases over a period of 25 months were extracted from the National Disease Reporting System (NDRS) and analyzed. An interrupted time series (ITS) technique was used to detect changes in HFMD incidence rates in terms of level and slope between declining incidence periods of the three years.

Results Over 3.58 million HFMD cases younger than 5 years were reported to the NDRS between May 1, 2008, and May 31, 2011. Males comprised 63.4% of the cases. ITS analyses demonstrated a significant increase in incidence rate level ($P<0.0001$) when comparing the current period with the previous period. There were significant changes in declining slopes when comparing 2010 to 2009, and 2010 to 2008 (all $P<0.005$), but not 2009 to 2008.

Conclusion Incremental changes in incidence rate level during the declining incidence periods of 2009 and 2010 can potentially be attributed to a few factors. The more steeply declining slope in 2010 compared with previous years could be ascribed to the implementation of more effective interventions and preventive strategies in 2010. Further investigation is required to examine this possibility.

Key words: Hand, foot, and mouth disease; Epidemic; Infectious disease; Disease surveillance; Interrupted time series analysis

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INTRODUCTION

Hand, foot, and mouth disease (HFMD) is a common contagious condition caused by intestinal viruses of the Picornaviridae family. The most common viral strains are Coxsackievirus A16 (CA16) and Enterovirus 71 (EV71), in which CA16 is the dominant strain for HFMD[1]. HFMD mostly affects children younger than 5 years, and its usual incubation period ranges from 3 to 7 days. The most common signs and symptoms of HFMD include fever, headache, vomiting, fatigue,

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malaise, sore throat, oral vesicular lesions, skin vesicular lesions and oral ulcers. The skin lesions present predominately on the hands and feet. Usually, HFMD is a mild condition. However, severe cases with meningitis, encephalitis, polio-like paralysis and subsequent death occasionally occur[2].

The epidemiologic features of HFMD can appear in an epidemic or sporadic fashion. HFMD epidemics are usually due to EV71[3-4]. Several severe outbreaks of HFMD have recently been reported in Asian countries. Japan has experienced nationwide epidemics since the first HFMD case was diagnosed in Tokyo in 1963[5-6]. In 1997, an outbreak caused mainly by EV71 was reported in Malaysia[7]. Between 2006 and 2007, there was an HFMD epidemic in Singapore, and the cumulative incidence of HFMD in children younger than four years reached 6%[8]. In China, HFMD cases were sporadically reported in Shanghai in 1981. Subsequently, several sporadic cases were seen in Beijing, Hebei, Tianjin, Fujian, Jilin, Shandong, Hubei, Xining, Guangdong, and Taiwan. A few outbreaks occurred in Dandong, Wuhan, and Hong Kong during 1983 and 1987. In the last four years, the prevention and control of HFMD became an issue in certain parts of China, and the HFMD epidemics in Shandong, Anhui, Henan, and Zhejiang have generated national concern.

Both sporadic cases of HFMD and epidemics have been observed in countries with a temperate climate, and occur most often during the warmer months[9]. Statistics published by the Chinese Center for Disease Control and Prevention (China CDC) demonstrate that epidemics in Mainland China commence in February, continue to increase in March, peak in April or May, and subsequently decline until the end of December or the following January.

On May 2, 2008, HFMD was upgraded to a Class C communicable disease, and became managed under the “Law on the Prevention and Control of Infectious Diseases” that was passed by the tenth NPC Standing Committee of the People's Republic of China. Since then, nation-wide cases of HFMD have been officially reported to the National Diseases Reporting System (NDRS) of China CDC. In this report, data covering a period of 25 months, from May 1, 2008, to May 31, 2011, are used. The analysis was limited to children younger than 5 years, because these children are the most affected by HFMD.

Interrupted time series (ITS) designs can be used to assess the impact of a policy change or intervention[10]. They are especially applied to routine surveillance data that have no obvious control group. Randomized experiments are perceived as the gold standard by which effectiveness is measured in a study. However, two alternative types of quasi-experimental designs-controlled before and after studies and ITS studies-are recognized by the Effective Practice and Organization of Care Group as improving the quality of information for decision makers[11]. ITS designs use routine monitoring data collected at equally spaced intervals of time before and after an intervention, with the period before intervention serving as a control group. This makes an ITS design a much more practical option in many settings, even though the allocation of subjects is not randomized. When experimental study is not possible, an ITS study can provide a robust method of measuring the effect of an intervention[11].

There are two different types of ITS designs, one is simple and the other is complex. A simple ITS design has only one group. The data are collected at different time points with equal time intervals and the period before the intervention is treated as the control. A complex ITS design has at least two groups, one of them serves as a concurrent control group. The ITS approach has been used to assess the effectiveness of a variety of interventions in various fields such as in environmental, financial, and health sciences. However, it had yet to be used for infectious diseases data from the NDRS. ITS designs are appropriate for this type of data, because while it is not possible to conduct a baseline survey, a few years of data are available to evaluate the impact of an intervention.

The first objective of this report was to examine changes in the level and slope of HFMD incidence during the declining incidence periods (May to December or the following January) of 2008, 2009, and 2010 using a simple ITS design when only retrospective surveillance data are available. First, the report identifies differential patterns in the declining incidence periods in terms of both level and slope of HFMD incidence. The second objective was to provide researchers with a statistical methodology for analyzing administrative routine data without an apparent control group.

MATERIALS AND METHODS

The NDRS was developed and implemented by China CDC on January 1, 2004. By the end of 2008, the NDRS had covered all levels of centers for disease control and prevention, 97% of county and high-level hospitals (more than 80 000 healthcare facilities) and 82% of township hospitals in mainland China. Individual cases of notifiable infectious diseases from all over China were directly reported to the NDRS within 24 h of diagnosis through the internet[12]. Details of system maintenance, routine data quality checking and yearly auditing of field data are reported elsewhere[13-14]. The 2010 China CDC report on NDRS data quality showed that the "zero" reporting rate at the statistical unit of districts (counties) was 0.06%; the rate of timely-reported cases was 99.22%; the monthly average rate of repeated reports was 0.02%; the rate of physicians filling out cards was 95.62%; and the rate of filling in the parents' name for children aged ≤ 14 years was 92.91%. Relative to previous years, the above indicators of reporting quality were improving.

In the present analysis, the definition and clinical diagnostic criteria of HFMD set up by China CDC in the Hand, Foot, and Mouth Disease Control and Prevention Guideline, Version 2008[15] were used. HFMD data for the period between May 1, 2008, and May 31, 2011, were extracted from the NDRS. More than 4 million individual cases were reported to the system during the study period. Population data for corresponding years were obtained from the Chinese Health Statistical Yearbook and the China Statistical Yearbook[16-19].

Data were aggregated monthly and monthly HFMD incidence rates were calculated and expressed as number of cases per 10,000 persons. Graphs were used to present and evaluate patterns in HFMD incidence rates from May 1, 2008, to May 31, 2011. An ITS design was applied to analyze changes in both level and slope for the declining incidence periods of 2008, 2009 and 2010.

An ITS design was also used to detect whether interventions had an effect on incidence rates that was significantly greater than the underlying secular trend[20]. This analysis referred to the declining period of 2008 as the secular trend. ITS analyses were then performed to monitor trends in the corresponding periods of the years 2009 and 2010. To model changes in level and slope, the following multivariate linear model was fitted to the data:

$$Y_t=\beta_0+\beta_1X_1+\beta_2X_2+\beta_3X_3+\varepsilon_t \qquad (1)$$

Here, $\beta_0$was the intercept, X_1 was a counter variable for time (t=1,2,…,n), X_2 was a dummy variable, in which X_2=0 for observations in 2008 and X_2=1 for observations in 2009 or 2010; X_3=0 for observations in 2008, X_3= X_1 for observations in 2009 or 2010; and ε_t was the error term.

In 2008 (pre-intervention), X_2= X_3=0, the model was as follows:

$$E(Y_t)=\beta_0+\beta_1X_1 \qquad (2)$$

β_0 represents the intercept of the 2008 line or pre-intervention; β_1 represents the slope of the 2008 line. In 2009 or 2010 (post-intervention), X_2=1 and X_3= X_1, then for the 2009 or 2010 line (post-intervention) the model is as follows:

$$E(Y_t)=(\beta_0+\beta_2)+ (\beta_1+\beta_3)X_1 \qquad (3)$$

Hereby, the constant or intercept was adjusted byβ_2 and the slope was adjusted byβ_3, indicating changes in level and slope (trend), respectively. The following chart (Figure 1) concisely illustrates the mechanism of the ITS model with respect to changes in level and trend.

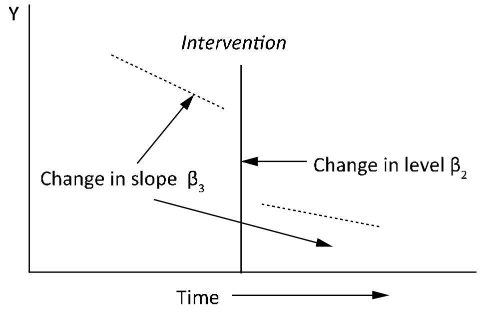

Figure 1. The changes in level and trend estimated by an ITS regression analysis.

In the above model, the assumptions about the error term (ε_t) were (1) zero mean; (2) constant variance; (3) no correlation with X_1 (counter variable for time); (4) no autocorrelation; and (5) normally distributed. The assumption of no autocorrelation is extremely important and most likely not to be met when using time series data. Therefore, prior to performing ITS analyses, data were checked for serial-correlation or autocorrelation using the Durbin Watson method[21]. Results showed that first-order autocorrelation values were just above 0.5 and the Durbin-Watson statistics were less than 2, suggesting a moderate positive autocorrelation in the series[21]. Therefore, serial correlation needed to be corrected for. The SAS procedure (Proc Autoreg) was used to correct for the first-order autocorrelation, with the YW method, which specifies Yule-Walker estimates in the model selection.

To control for the different effects of "interventions" in different provinces, the incidence rate data were reanalyzed using the ITS technique with the variable of province as 31 dummy variables in the model; the results and parameters of model fit are given in Table 2.

Statistical analyses were carried out using the Statistical Analytical System (SAS Institute Inc., Cary, NC, USA). A critical value of 0.05 was set for rejection of the null hypothesis.

RESULTS

Over four million cases of HFMD were reported to the NDRS of China CDC between May 1, 2008, and May 31, 2011. Of them, over 3.58 million cases were younger than 5 years, accounting for 88.6% of all cases. Of those younger than 5 years, 63.38% were male.

Figure 2 presents incidence rates by month and gender. Peak incidence rates occurred in May of 2008 and 2010, and in April of 2009. The floor rates were seen in February of 2010 and 2011, and in January of 2009. It took only three months for the peak rate to reach the floor rate each year.

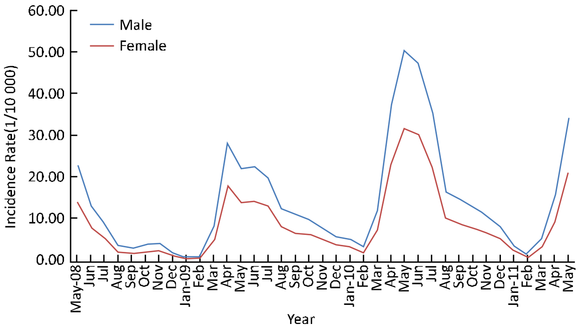

Figure 2. HFMD incidence rates from May 1, 2008, to May 31, 2011.

The ITS analysis demonstrated a significant increase in level for males, females and all cases (*P*<0.0001) when comparing the current period with the previous period (Table 1), suggesting a significantly higher incidence rate in the later period.

The changes in declining slopes were statistically significant when comparing 2010 to 2009, and 2010 to 2008 (all *P*<0.005). However, a change in slopes between 2009 and 2008 was not evident.

Table 1. Parameter Estimates of Comparisons between Decreasing Incidence Periods of 2008, 2009, and 2010

	Change in Level (X_2)		**Change in Slope (X_3)**		**Parameters of Model Fit**			
Comparisons	Parameters (Std. error)	*P*-value	Parameters (Std. error)	*P*-value	1st Order Autocorrelation	Durbin-Watson D	Root MSE	R^2
Period 2 *vs*. Period 1								
Male	32.27 (5.02)	<0.0001	-0.26 (0.49)	0.5987	0.367	0.904	3.073	0.884
Female	20.82 (3.13)	<0.0001	-0.21 (0.31)	0.4953	0.341	0.965	1.919	0.886
Subtotal	26.80 (4.11)	<0.0001	-0.24 (0.40)	0.5581	0.357	0.926	2.519	0.885
Period 3 *vs*. Period 2								
Male	81.55 (9.56)	<0.0001	-3.00 (0.71)	0.0006	0.521	0.863	4.894	0.89
Female	52.04 (6.29)	<0.0001	-1.93 (0.47)	0.0007	0.522	0.864	3.218	0.884
Subtotal	67.36 (7.99)	<0.0001	-2.48 (0.60)	0.0006	0.521	0.864	4.088	0.888
Period 3 *vs*. Period 1								
Male	81.08 (10.15)	<0.0001	-3.26 (0.97)	0.0042	0.52	0.786	5.694	0.879
Female	52.09 (6.57)	<0.0001	-2.14 (0.63)	0.0038	0.525	0.784	3.687	0.876
Subtotal	67.15 (8.43)	<0.0001	-2.72 (0.80)	0.004	0.522	0.785	4.73	0.878

Note. Root MSE is the estimate of the standard deviation of the error term and is calculated as the square root of the mean square error. R^2 indicates the proportion of total variation attributed to the model fit. The value of Durbin-Watson D lies between 0 and 4; if the value is less than 2, there is evidence of positive serial correlation.

Table 2 presents parameter estimates of model fit after accounting for the different intervention efforts in different provinces. Changes in level and slope for all fitted models did not alter the statistical significance, although the parameters of model fit, such as the coefficients of determination (R^2) were inferior to those of the models without adjustment for the provincial variable.

Table 2. Parameter Estimates of Comparisons between Decreasing Incidence Periods after Adjustment for Provincial Variation

	Change in Level (X_2)		**Change in Slope (X_3)**		**Parameters of Model Fit**			
Comparisons	Parameters (Std. error)	*P*-value	Parameters (Std. error)	*P*-value	1st Order Autocorrelation	Durbin-Watson D	Root MSE	R^2
Period 2 *vs.* Period 1								
Male	25.53 (2.58)	<0.0001	0.13 (0.25)	0.6072	0.203	1.585	8.915	0.548
Female	16.63 (1.68)	<0.0001	0.05 (0.17)	0.75	0.22	1.549	5.815	0.539
Subtotal	21.26 (2.14)	<0.0001	0.09 (0.21)	0.6648	0.21	1.57	7.405	0.544
Period 3 *vs.* Period 2								
Male	84.70 (4.96)	<0.0001	-3.30 (0.37)	<0.0001	0.545	0.907	14.355	0.567
Female	55.40 (3.31)	<0.0001	-2.18 (0.25)	<0.0001	0.554	0.89	9.582	0.551
Subtotal	70.59 (4.16)	<0.0001	-2.76 (0.31)	<0.0001	0.549	0.899	12.035	0.561
Period 3 *vs.* Period 1								
Male	80.42 (4.58)	<0.0001	-3.20 (0.44)	<0.0001	0.526	0.932	14.537	0.594
Female	52.86 (3.04)	<0.0001	-2.15 (0.29)	<0.0001	0.532	0.918	9.64	0.582
Subtotal	67.16 (3.83)	<0.0001	-2.69 (0.36)	<0.0001	0.529	0.926	12.151	0.59

Yule-Walker methods were used to correct for the first-order autocorrelation in the series; nevertheless, the results did not change for the analyses in Tables 1 and 2 (data not shown).

To further investigate why the R^2 of models with adjustment for the area variable were not as good as those without adjustment for the area variable, we examined the incidence pattern in each province, and found that a few areas, such as in Fujian, Hainan, and Tibet (shown in Figures 3-5), did not follow the general HFMD pattern, i.e. peak rates in April or May and floor rates in January or February (as shown in Figure 2). This could partially explain the lack of goodness-of-fit of models with adjustment for the area variable, as indicated by a smaller R^2.

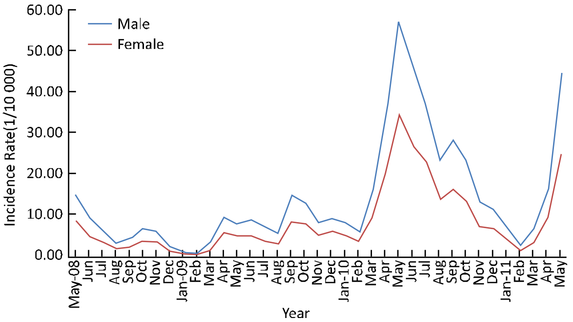

Figure 3. HFMD incidence rates from May 1, 2008, to May 31, 2011, in Fujian.

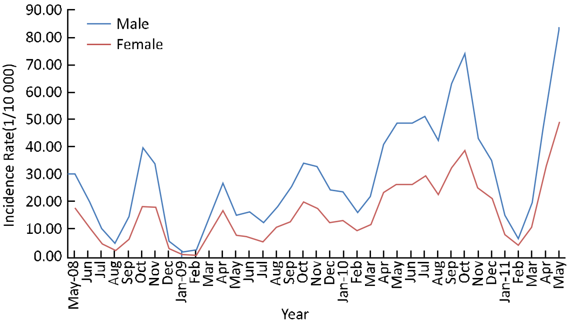

Figure 4. HFMD incidence rates from May 1, 2008, to May 31, 2011, in Hainan.

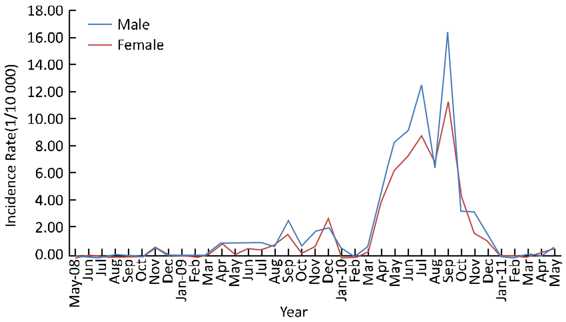

Figure 5. HFMD incidence rates from May 1, 2008, to May 31, 2011, in Tibet.

To show the details for more provinces, especially with those with a substantial number of cases, data of three provinces (Guangdong, Zhejiang, and Shandong) that had the most HFMD cases during the study period were chosen to be presented in Figures 6-8. It can be seen that all three provinces demonstrated similar patterns to the general pattern in Figure 2, except for Zhejiang, in which HFMD incidence peaked in October.

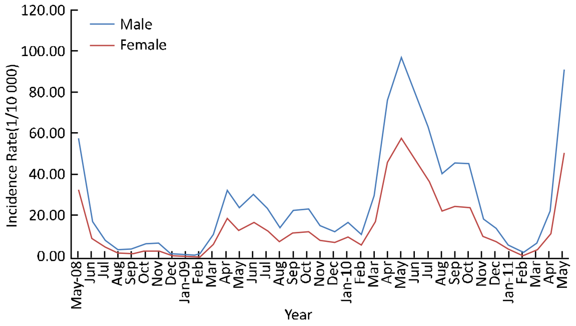

Figure 6. HFMD incidence rates from May 1, 2008, to May 31, 2011, in Guangdong

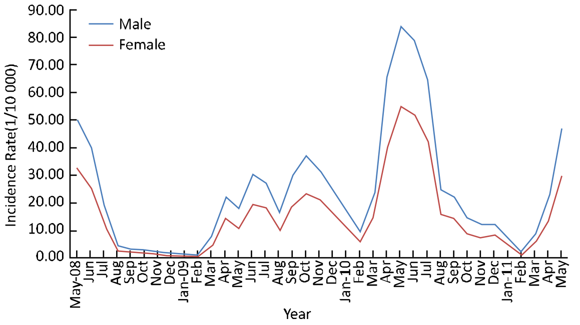

Figure 7. HFMD incidence rates from May 1, 2008, to May 31, 2011, in Zhejiang.

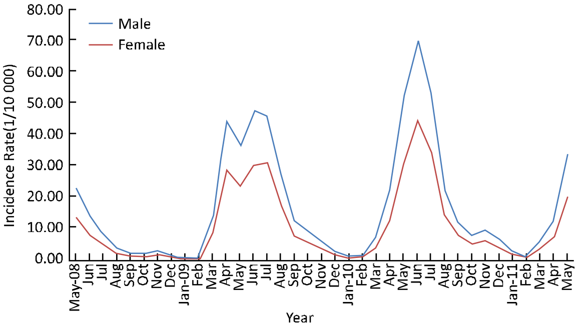

Figure 8. HFMD incidence rates from May 1, 2008, to May 31, 2011, in Shandong

DISCUSSION

The Guidelines for Diagnosis and Treatment of HFMD were introduced soon after the Class C communicable disease management procedure for HFMD was announced on May 2, 2008, by the Ministry of Health. Since then, HFMD cases across China have been officially reported to the NDRS. In addition, a series of actions have been taken to improve the quality of data reporting, including a national training conference on data entry, annual field audits, routine data quality checking, and data quality reporting at national, provincial, and municipal levels. Therefore, the data were viewed as being of high quality with respect to accuracy, timeliness, comparability, usability and relevance following the introduction of the Class C communicable disease management procedure for HFMD.

A report published by China CDC on June 3, 2008, illustrated that the HFMD incidence rate peaked on May 12, 2008, leveled off during the following week, and then declined until the end of the year. From our findings, the 2009, peak incidence occurred in April a few weeks ahead of the 2008 peak; the 2010 peak returned to May. Based on available and reliable NDRS data, ITS analyses[20-21] were used to compare changes in the decreasing incidence periods of 2008, 2009, and 2010 in terms of both level and slope. The ITS results demonstrated that abrupt changes (increases) in level were statistically significant for all comparisons in males, females and all cases, indicating a higher average incidence in the later year than in the previous year. The slope changes (decreases) were statistically significantly steeper in 2010 compared with 2009 in males, females and all cases, implying that effective prevention measures were implemented. The slope changes (decreases) between 2009 and 2008 were not statistically significant for any comparison.

The phenomenon of a high HFMD incidence during the declining incidence periods of 2009 and 2010 could potentially be attributed to three factors. First, health facilities might have reported more HFMD cases in 2009 and 2010 because of the provision of further training, education about reporting and/or public and political attention. However, to our knowledge, HFMD preventive strategies, the reporting culture, statistical rules, definitions and guidelines for the reporting of HFMD remained unchanged over the three years. Therefore, this explanation could only account for a small proportion of the elevated level of HFMD incidence in 2009 and 2010. Second, HFMD broke out more often in the last few years, and the pool of silent infections became considerably large. Furthermore, there could be a lack of cross-immunity of various types of HFMD; therefore, more cases would present in the current compared with the prior year. This hypothesis could be confirmed by examining changes in the sub-genogroups of EV71 or CA16 over time in the region. Third, neonates are added to the sensitive pool each year. These neonates have lower level of antibody, and are susceptible to infection. However, birth rates did not significantly increase or decrease during the study period, so there was a uniform number of neonates over the three years. Finally, HFMD presents a seasonal pattern every 2-3 years[22]. Therefore, the years 2009 and 2010 may represent the peak of an epidemic cycle. The phenomenon of high incidence rates in 2008 was also noted when compared with those of 2007. Because HFMD was not included in the Class C communicable disease register in 2007, the elevated incidence rates in 2008 may be partially attributed to underreporting in 2007.

No difference was found between the incidence rate slopes of 2009 and 2008, possibly because of the short time series. Nine points for 2008 and eleven for 2009 constitute a short period, which might lead the fitted model to have less confidence, increased standard errors and type I error rate, and reduced statistical power[19]. Resultantly, the model was not able to detect autocorrelation or secular trends. A potential solution for this issue is to use weekly or biweekly data to examine the hypothesis. This lack of change in incidence trends implied that no more effective “interventions” were implemented in 2009 compared with 2008. Conversely, the steep decrease in the slope of 2010 compared with that of 2009 implied that control measures might have been effectively implemented in 2010, provided that the factors associated with HFMD risk remained unchanged.

Routine monitoring data were used in this report. One should be aware of ongoing intervention programs, whose effects could not be differentiated from one another within a region, because interventions or preventive strategies were beyond of the control of the researchers in this situation. Moreover, different provinces may have their own procedures for HFMD prevention, and the role of these interventions or preventive strategies may not be detected, if they existed. To control for the different effects of interventions in different provinces, the incidence rate data were reanalyzed after adjustment for area variation using the ITS technique. The estimated parameters and standard errors did not change considerably, However, R^2, a parameter of model fit, decreased from almost 90% to around 55%, because the distribution of HFMD cases in a few provinces violated the general pattern shown in the whole dataset. Nevertheless, data of three provinces (Guangdong, Zhejiang, and Shandong) that had the most HFMD cases during the three years demonstrated similar patterns to the general pattern shown in Figure 2, except for Zhejiang, which experienced a peak in October. These might be a predominant demonstration of the general pattern.

Model fit would definitely be improved after data from the provinces showing different patterns were excluded. However, our objective was to present a national profile of HFMD cases. Finally, a low percentage of HFMD cases were laboratory-confirmed, possibly leading to misclassification of the disease. It is impossible to confirm all nation-wide cases by laboratory testing in China at present.

In general, the incremental changes in incidence rate level during the declining incidence periods of 2009 and 2010 could be attributed to more case reporting, silent infections in the previous year, the peak of an epidemic cycle in 2009 and 2010, and/or neonates being added to the sensitive pool. The steeper declining slope during the decreasing incidence period in 2010 compared with previous years may be ascribed to more effective interventions and preventive strategies, or abrupt changes of risk factors associated with the development of HFMD, such as air temperature, atmospheric pressure, humidity level, and/or socioeconomic indicators. Further investigation is required to address this possibility.

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