RESEARCH ARTICLE

The impact of anti-COVID-19 nonpharmaceutical interventions on hand, foot, and mouth disease—A spatiotemporal perspective in Xi'an, northwestern China

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Abstract

Growing evidence has shown that anti-COVID-19 nonpharmaceutical interventions (NPIs) can support prevention and control of various infectious diseases, including intestinal diseases. However, most studies focused on the short-term mitigating impact and neglected the dynamic impact over time. This study is aimed to investigate the dynamic impact of anti-COVID-19 NPIs on hand, foot, and mouth disease (HFMD) over time in Xi'an City, northwestern China. Based on the surveillance data of HFMD, meteorological and web search data, Bayesian Structural Time Series model and interrupted time series analysis were performed to quantitatively measure the impact of NPIs in sequent phases with different intensities and to predict the counterfactual number of HFMD cases. From 2013 to 2021, a total number of 172,898 HFMD cases were reported in Xi'an. In 2020, there appeared a significant decrease in HFMD incidence (−94.52%, 95% CI: −97.54% to −81.95%) in the first half of the year and the peak period shifted from June to October by a small margin of 6.74% compared to the previous years of 2013 to 2019. In 2021, the seasonality of HFMD incidence gradually returned to the bimodal temporal variation pattern with a significant average decline of 61.09%. In particular, the impact of NPIs on HFMD was more evident among young children (0–3 years), and the HFMD incidence reported in industrial areas had an unexpected increase of 51.71% in 2020 autumn and winter. Results suggested that both direct and indirect NPIs should be implemented as effective public health measures to reduce

infectious disease and improve surveillance strategies, and HFMD incidence in Xi'an experienced a significant rebound to the previous seasonality after a prominent decline influenced by the anti-COVID-19 NPIs.

1 | INTRODUCTION

Hand, foot, and mouth disease (HFMD) is a common infectious disease caused by more than 20 enteroviruses pathogens that mainly involve Enterovirus 71 (EV71) and Coxsackievirus A16 (CVA16) serotypes.[1] HFMD is characterized by a sudden onset of fever with vesicular rashes on hands, feet, and buttocks and ulcers in the oral mucosa. Most patients infected with HFMD via close contact, respiratory droplets, or fecal–oral route could recover spontaneously within a week; however, in a few severe cases, cardiopulmonary complications can result in death.[2,3] The susceptibility and severity of HFMD are closely associated with age, and children under 5 years are identified as the most susceptible targets, especially in densely populated urban areas.[4] Since 1997, the Asia-Pacific region has become the most vulnerable area to HFMD worldwide with China as the worst affected country.[2] In China, HFMD accounted for the largest percentage of notifiable infectious diseases from 2013 to 2018, and 2,353,310 cases were reported in 2018 (http://www.nhc.gov.cn/jkj/). To restrain the continuous prevalence of HFMD, the Chinese government has adopted a series of prevention and control measures, including vaccines, health education, and hand hygiene.[5] Vaccination has been proven to be an effective measure to reduce the incidence of HFMD, and in recent years, EV71-related HFMD incidence steadily decreased due to the advent of inactivated monovalent EV71 vaccines and an extensively developed three-level surveillance laboratory network.[2,6] Nevertheless, there has been a growing number of Coxsackievirus-relative HFMD cases after 2017,[6,7] which could engender a possible resurgence of the HFMD epidemic in the absence of targeted measures.

Effectively reducing the incidence of HFMD is still a critical issue among researchers and public health administrators. At the moment, lessons from measures against coronavirus disease 2019 (COVID-19) might provide a way. In 2020, the COVID-19 pandemic spread globally and led to disastrous and unforeseen consequences in most aspects of human society. To overcome the COVID-19 crisis, governments worldwide implemented a series of corresponding measures using nonpharmaceutical interventions (NPIs) (e.g., home quarantine, reducing social distancing, travel restrictions, and masking), which have mitigated the magnitude and geographical scope of COVID-19 propagation.[8,9] Surprisingly, studies revealed that not only respiratory infectious diseases but also intestinal infectious diseases cases dramatically decreased in multiple regions during the COVID-19 pandemic.[10–12] This indicated that the positive effects of anti-COVID-19 measures extended to several other communicable diseases,[13–15] and were also confirmed in China.[16] Specifically, there was a more dramatic decline in HFMD incidence than in other intestinal infectious diseases in 2020.[17] In addition, due to the large-scale school closure, the reported cases of HFMD decreased more rapidly in children compared to other population groups, and strikingly, the number of local HFMD cases also varied between cities.[16,18] This heterogeneous impact of NPIs could be attributed to differences in population mobility, geographical locations, and sociodemographic characteristics, which should require relevant specific policies for each region.[19,20] While anti-COVID-19 NPIs have been proven effective in HFMD, the intensity of NPIs adopted by the Chinese government has changed in distinct epidemic stages to revive the economy—as opposed to remaining high at all times. Accordingly, the role of NPIs in altering short-term (i.e., the early emergency response with strict anti-COVID-19 measures) and potential long-term (i.e., the stage of normalization of epidemic prevention and control) dynamics of HFMD must be quantified to develop more targeted measures. These insights can be simultaneously drawn from the fight against the COVID-19 pandemic and emphatically implemented to prevent and control HFMD in the postpandemic era. However, few studies have investigated the impacts of anti-COVID-19 NPIs on HFMD from a long-term perspective. Moreover, considering the geographical heterogeneity, the influence of NPIs during the COVID-19 pandemic on the spatial patterns of HFMD incidence in high-risk areas of China is also uncertain.

Therefore, we conducted a retrospective epidemiological case study of 9-year HFMD surveillance in Xi'an, the largest regional central city in northwestern China with a serious prevalence of HFMD.[21] The main aims were to investigate how anti-COVID-19 NPIs can affect the HFMD epidemic in a large city with a population of over 12 million and to quantitatively assess the short-term and potential long-term impacts of NPIs in the postepidemic era. Furthermore, based on different mathematical models we also examined the geographical and populational heterogeneity of the detected impacts. Research into these problems will contribute to the formulation of HFMD prevention and control measures in large cities.

2 | MATERIALS AND METHODS

2.1 | Study area and anti-COVID-19 NPIs

As the largest city in Northwest China, Xi'an (105°29'–115°15' E, 31°42'–39°35' N) has a total area of 10,752 km^2, consisting of 13 districts and counties (Figure S1). The total population in 2021 was 12.95 million (http://www.xa.gov.cn/). Xi'an is surrounded by Qinling Mountains in the south and experiences four distinct seasons with a subhumid warm temperate continental monsoon climate. Annually, the city typically receives 528.3–716.5 mm of precipitation with an average temperature of 13.1–14.3 °C. The seasonality of HFMD differs geographically which shows a bimodal seasonality of May and October in certain cities in southern China, and a unimodal peak in June in northern China.[22] Two peak times for HFMD incidence are recognized in Xi'an with the larger in May and the second in October, which is significantly different from those observed in other areas of northern China.[21] Concomitant with rapid urban development, Xi'an has grown as a tourist city characterized by a high population density and mobility, which has posed great pressure on the epidemic prevention and control of the city. Although the number of HFMD cases in Xi'an initially declined after the outbreak of COVID-19, it has rapidly rebounded as schools resumed classes (http://jyt.shaanxi.gov.cn/). Thus, it is of great necessity to conduct this retrospective epidemiological study in such an important and representative study area.

The first confirmed case of COVID-19 in Xi'an was reported on January 23, 2020 and the local government immediately implemented a Level-I public health emergency response throughout the city on January 25, 2020 (http://xawjw.xa.gov.cn/). A series of prevention and control interventions, including closing schools, cancelling public events, and home quarantine was taken following the emergency response. As of February 22, 2020, the strict anti-COVID-19 measures reduced the number of new confirmed cases and asymptomatic carriers in Xi'an to zero and the emergency response was accordingly revised down to Level-III on February 28, 2020 (http://xawjw.xa.gov.cn/). Residents in Xi'an gradually returned to normal life after April 2020. Particularly, on June 8, 2020, all kindergartens, primary schools, middle schools, high schools, and colleges in Xi'an were permitted to resume classes. During the period of normalization of epidemic prevention and control, all reported cases were imported from overseas until one local was confirmed positive on January 28, 2021 (http://sxwjw.shaanxi.gov.cn/), which prompted the Xi'an government to immediately take prevention and control measures in schools and communities (http://edu.xa.gov.cn/). After this short-term reintroduction of the COVID-19 pandemic, primary schools and kindergartens in Xi'an were allowed to start the spring semester as planned. At the end of our research period, the pandemic in Xi'an flared again and 1451 confirmed cases have been reported in this outbreak in December 2021 (http://sxwjw.shaanxi.gov.cn/).

2.2 | Data sources

Data of HFMD cases from January 2013 to December 2021 were provided by the Center for Disease Control and Prevention of Xi'an through the National Notifiable Infectious Diseases Reporting Information System. The specific parameters noted in our research mainly involved diagnosis time, address, age, gender, occupation, and reporting institutions, as well as pathogenic test results in sampled HFMD cases. Based on a previous study on the association between meteorological factors and the seasonal transmission of HFMD,[22] six meteorological variables in Table S1 were collected from the National Meteorological Information Centre for Xi'an (http://data.cma.cn/). In addition, web search data were used as an effective tool for obtaining information on infectious diseases complementary to the traditional monitoring systems. Previously, Baidu Search Index (BSI), which helps track disease-related trends based on the search behaviors of online users on a specific search engine, has been successfully applied to improve the accuracy of HFMD prediction.[3] Thus, we selected five indexes using the keywords of HFMD from the shared platform of the BSI (https://index.baidu.com/) with detailed descriptions of these indexes in Table S1. After data cleaning and classification, we aggregated the HFMD information and relevant influential factors into monthly and weekly series. Weekly HFMD cases in 13 districts and counties in Xi'an were collated to further analyze the spatial heterogeneity among different areas. Relevant statistical data at the county level were acquired from Xi'an Statistic Yearbooks (http://tjj.xa.gov.cn/). Vector boundaries for the study area were obtained from the basic geographic database in the National Catalogue Service For Geographic Information of China (https://www.webmap.cn) and base maps from the ArcGIS Online platform of ESRI (https://server.arcgisonline.com/).

2.3 | Statistical analysis

To compare the dynamic prevalence of HFMD in Xi'an, we calculated the differences between the weekly HFMD cases of 2020, 2021, and previous years. Considering the epidemic season of HFMD in Xi'an, relative changes compared with the average HFMD cases of 2013–2019 were calculated during the weeks numbered 1–36 and 37–52 for 2020 and 2021, respectively. The gender, age group (0–3; 3–6; >6 years), and counties where HFMD cases occurred were used to derive specific results via classifications. Counties and districts in Xi'an were first categorized into three classes in terms of relative changes, before correlating the incidence with the relevant factors for these three classes. To assess how HFMD transmission was affected by NPIs, we applied a three-step time-series analysis to identify the change-points, predict the counterfactual number of HFMD cases, and investigate the quantitative effects of the interventions emerging in the postpandemic era.

2.3.1 | Bayesian Estimator of Abrupt change, Seasonality, and Trend (BEAST)

The first step was to identify the change points of the HFMD time series for the whole research period, which can be used to further define distinct epidemic periods by combining the implementation of antipandemic regulations in Xi'an. The Bayesian model averaging scheme is a promising method to capture rich variations in trend, seasonality, and change points since it has been improved by integrating numerous optimization models in time-series decomposition.[23] Specifically, the superior model BEAST can manage the uncertainty by selecting the optimal candidate model and simultaneously relating the change, seasonality, and trend.[24] Moreover, the probability that a disturbance occurs at any specific time point can also be estimated to identify the potential changes in the time series. The BEAST modeling of the weekly and monthly HFMD time series was performed using the package "Rbeast" v0.2.2 (https://CRAN.R-project.org/package=Rbeast) in R v4.0.4.

2.3.2 | Bayesian Structural Time Series (BSTS)

The time-series model used to predict the expected number of HFMD cases is the BSTS which is capable of separately extracting the trend, seasonal, and regression components based on stochastic state-space.[25] The BSTS model can be described by Equations (1)–(3) [26] as follows:

$$y_t = \mu_t + \tau_t + \beta^T x_t + \varepsilon_t, \tag{1}$$

$$\mu_t = \mu_{t-1} + \delta_{t-1} + u_t, \tag{2}$$

$$\delta_t = \delta_{t-1} + \upsilon_t, \tag{3}$$

where y_t is the observation in week t of the HFMD time series and follows a Poisson distribution; μ_t denotes the latent state evolving over the time t with the dynamic slope δ_t; τ_t is the seasonal component; x_t is a contemporaneous set of meteorological factors; while BSIs and β^T represent the regression coefficients. The Markov chain Monte Carlo sampling algorithm was utilized to simulate the parameter values from the posterior distribution and 100,000 iterations were run with a burn-in of 20,000 iterations in our study. BSTS models finally yielded the expected HFMD cases with two types of covariates as the input for further regression analysis. More applicable models specific to different counties and age groups were also developed with meteorological factors because of deficient corresponding BSIs. Next, we calculated the symmetric mean absolute percentage error (SMAPE) and root mean square error (RMSE) of different models to test the prediction accuracy.[27] The aforementioned analyses were performed in R v4.0.4 using the package "bsts" v0.9.7 (https://cran.r-project.org/web/packages/bsts/index.html).

2.3.3 | Interrupted time series analysis (ITSA)

Most studies commonly adopt the ITSA method when examining the effectiveness of an intervention on public health problems.[28] ITSA has been identified as a feasible and effective way to capture the potential association between the results and its influential NPI strategies at the population level over a clearly defined period.[29] Given that ITSA is often designed based on regression methods, we adopted the regression components obtained by the BSTS model to conduct ITSA with properly controlled variables for the auto-correlation effect.

As three critical anti-COVID 19 regulations were implemented in Xi'an, we set three interrupted points in the HFMD time-series, while also dividing the forecast period (i.e., postintervention period) into three corresponding stages. The first stage is from the 5th week (Level-I public health emergency response) to the 23rd week (classes resumption) in 2020; the second stage covers the period from the 24th week in 2020 to the 3rd week (comeback of strict interventions) in 2021; and the third stage is from the 4th week in 2021 to the 52nd week in 2021. According to these three stages with different intervention intensities, the ITSA segmented regression model can be described by Equation (4) as follows:

$$Y_t = \beta_0 + \beta_1 T + \beta_2 X_1 + \beta_3 X_2 + \beta_4 X_3 + \beta_5 (T - T_1) X_1 \\ + \beta_6 (T - T_2) X_2 + \beta_7 (T - T_3) X_3, \tag{4}$$

where Y_t is the observation in week t; T is the timing sequence counting from 0 (with $T_1 - T_3$ as the interrupted points); X_1, X_2, and X_3 are three dummy variables that take 0 before three interrupted points and 1 after the interrupted points, respectively; the intercept term β_0 represents the initial level; the coefficient β_1 describes the basal change trend of the HFMD time series; the regression coefficients $\beta_2 - \beta_4$ are interpreted as the level changes following respective interrupted points; and $\beta_5 - \beta_7$ represent the slope changes. We performed 100,000 iterations and discarded 20,000 iterations using R v4.0.4 and the package "bsts" v0.9.7. The posterior distribution and inclusion probabilities (i.e., nonzero probabilities in iterations) of regression coefficients were applied to assess how the interventions influence the variation in HFMD cases to determine the optimal predictors.

3 | RESULTS

3.1 | Changes in HFMD incidence

From January 2013 to December 2021, a total number of 172,898 HFMD cases were reported in Xi'an. By comparing the differences in seasonal HFMD incidence in the time series for 2020, 2021, and the previous years, we found that in contrast to the characteristic trends for the average number of HFMD cases from 2013 to 2019, the primary characteristic peak disappeared in 2020 corresponding to the emergency response concurrently performed by the government
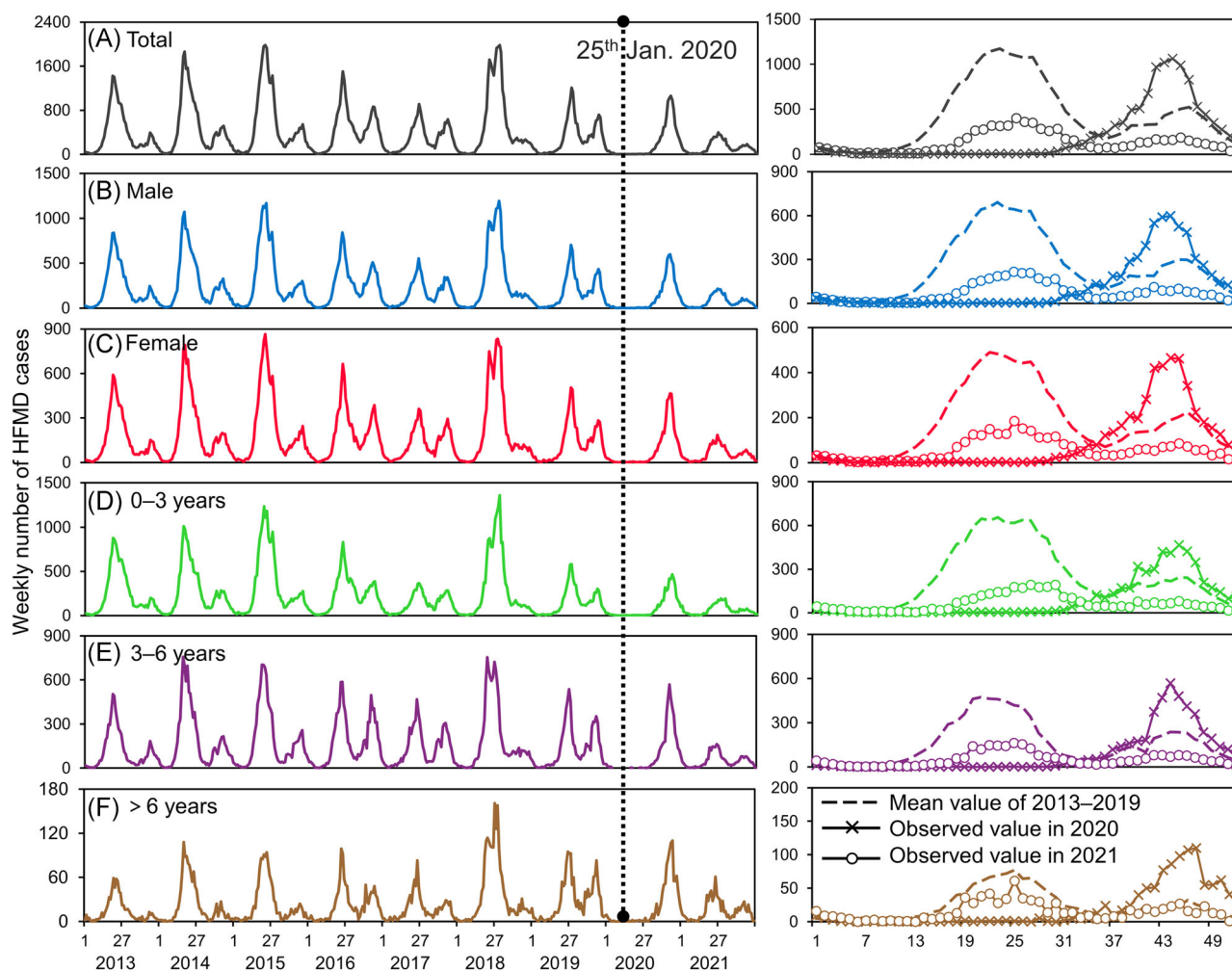
FIGURE 1 Weekly time-series of HFMD cases in Xi'an, 2013–2021. The number of cases in (A) total, (B) males, (C) females, and (D–f) the different age groups. HFMD, hand, foot, and mouth disease.

(Figure 1). Thereafter, the trend returned to a relatively lower level in 2021 exhibiting a similar trend to the variations in 2013–2019. Particularly, the rebounded secondary peak in 2020 was more significant for the age groups 3–6 years and >6 years, demonstrating a much higher value compared to both the first and secondary peaks in 2013 to 2019. The relative reduction of the number of HFMD cases was over 90% from the 1st to 36th week in 2020 and less than 75% in 2021 for all gender and age groups (Table S2). From the 37th week to the 52nd week in 2020, it is clear that the relative increments of the number of HFMD cases for both males and females were similar to the overall tendency in Xi'an; however, the incidence growth for the three age groups varied with the high age group showing the most dramatic change. In addition, the occurrence of HFMD demonstrated spatially dynamic distribution across the 13 counties within Xi'an (Figure S2) with the normal primary peak disappearing and the secondary one rising in 2020. According to the overall variations in weekly HFMD incidence for 2020 (Table S2), the 13 counties could be classified into three main categories: specifically, Class 1 with the four subdistricts Weiyang, Yanliang, Lintong, and Gaoling showed a lower decline in HFMD incidence compared to

Class 2 (Xincheng, Baqiao, Yanta, and Zhouzhi) and Class 3 (Beilin, Lianhu, Chang'an, Lantian, and Huyi).

Correlation analysis conducted at the county geographical scale was used to further explain why the spatial heterogeneity of HFMD incidence decreasingly varied in 2020. Since children under 5-year-old are the most vulnerable target group infected with HFMD, we focused more on aspects of education, medical resources, and birth rate which are closely related to the causes of HRMD infection. Three representative influential factors were selected as independent variables including the number of students in the primary school, the number of beds in the Community Healthcare Center, and the number of marriages (Figure 2B). The results showed that the HFMD incidence was significantly correlated with all three factors for the four counties consisting of Beilin, Lianhu, Chang'an, Lantian, and Huyi categorized to Class 3. The strongest correlation was found between the HFMD incidence and the number of beds in the Community Healthcare Center ($r = 0.78$; $p < 0.01$). However, for Class 1, only the linear relationship between the HFMD incidence and the number of students in the primary school was significant ($r = 0.55$; $p < 0.01$) while for Class 2 no significant relationships could be found for all
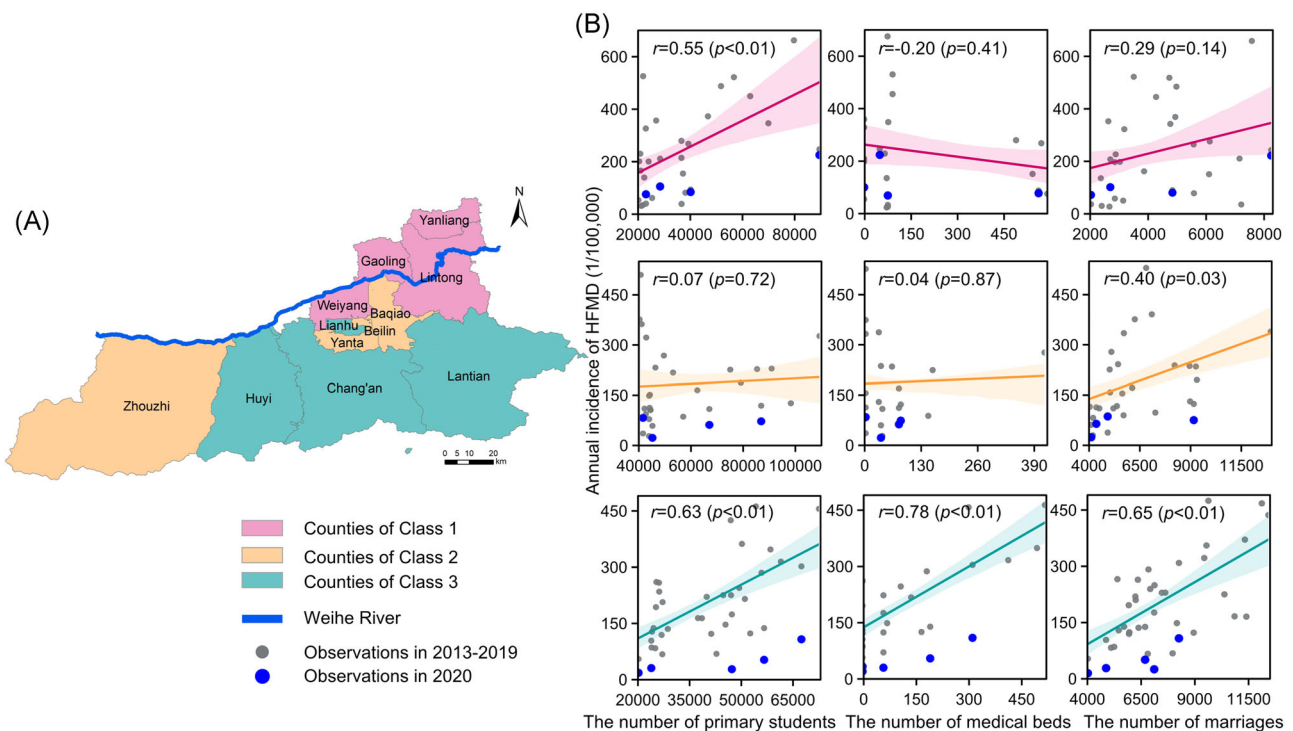
FIGURE 2 Association between HFMD incidence and potential factors for three classes of counties in Xi'an. (A) The spatial distribution of three classes of districts and counties in Xi'an. (B) Correlation coefficients between HFMD incidence and factors on education, public health services, and family. HFMD, hand, foot, and mouth disease.

three factors. Noteworthy, the spatial clustered patterns are shown by the counties of Class 1 (Figure 2A) aggregated in the northeast of Xi'an where it is cut through by the Weihe River where the decrease in HFMD incidence was not significant as in Classes 2 and 3 for 2020. This may be linked to the developed industries in the counties of Class 1.

3.2 | Changes in healthcare-seeking behaviors and pathogens of patients with HFMD

Moreover, we also conducted exploratory analysis on the temporal variations in the number of HFMD cases reported by four main types of medical institutions that accepted patients with HFMD during 2016–2021. This data helped provide some preliminary explanation of how these patients transformed their healthcare-seeking behaviors under the influence of NPIs. Figure 3 demonstrated that there was a phenomenal growth in the number of HFMD cases reported by maternal and child healthcare hospitals from 2016 to 2020, which remarkably reversed in 2021. By contrast, the number of HFMD cases reported by hospitals for infectious diseases neared zero in 2020 and remained stable at a low level in 2021. The temporal pie chart in Figure 3 illustrates that general along with children hospitals has consistently reported a high number of HFMD cases despite a slight fluctuation in 2020. In addition, Figure S3 exhibits changes in the detected enteroviruses serotypes (CVA16, EV71, and other enteroviruses) in pathogenic tests of laboratory-confirmed HFMD
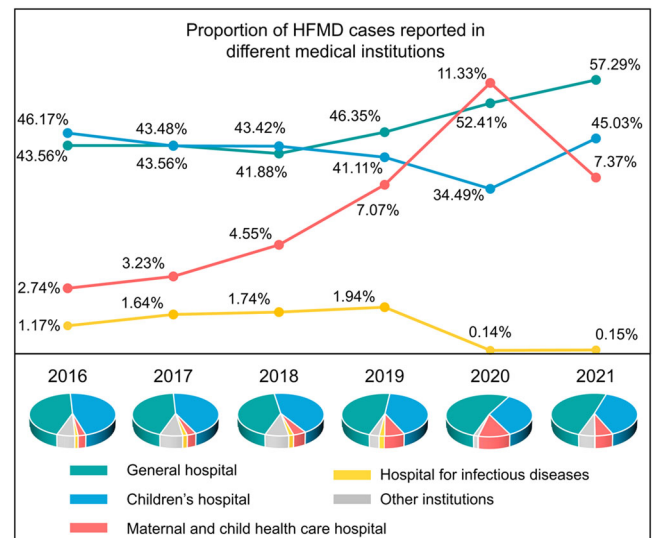

FIGURE 3 Changes in the proportion of HFMD cases reported in different medical institutions. The top four medical institutions with the highest proportion were selected to show changes during 2016–2021. HFMD, hand, foot, and mouth disease.

cases from 2016 to 2021. It reveals that from 2017 to 2019 the proportion of HFMD cases caused by CVA16 steadily increased from 12.78% to 40.73% before dropping to 11.87% after the COVID-19 outbreak (Figure S3). This implies that different serotypes of enteroviruses predominated at different periods.

3.3 | Impact of COVID-19 prevention and control interventions on HFMD

Though the changes in HFMD incidence can be detected by time-series analysis, the seasonal and trend dynamics of HFMD cases impacted by anti-COVID-19 NPIs in Xi'an are still unclear. Since it is essential to capture the change points of the HFMD time series, using the BEAST model we examined the number of HFMD cases in the time series at both monthly and weekly scales to identify significant change points in 2020. September 2019 and December 2020 were recognized as two critical seasonal change points for the monthly HFMD time series (Figure 4A) while December 1, 2020 was observed as one seasonal change point for the weekly HFMD time-series (Figure 4B). This is consistent with the conclusions in Section 3.1 that the seasonal patterns of HFMD incidence in Xi'an appear to significantly change at the beginning of both 2020 and 2021, with the latter getting back to the bimodal seasonality observed in previous years of 2013 to 2019. Concerning the trend dynamics, Figure 4 demonstrates that the number of HFMD cases has a continual decline in the trend after 2018 and then briefly rose in September–October 2020 to match with the characteristic secondary peak.

Furthermore, Figure 5 shows the simulation results derived from the BSTS models through identifying the differences between the reported number of HFMD cases and the predicted values based on two types of predictors: meteorological factors and BSI covariates. According to the obtained one step ahead prediction accuracy

(SMAPE: 0.005; RMSE: 0.473), fitting the results of the BSTS models could satisfy the requirements of subsequent analyses. Despite the overall simulation with meteorological factors as the predictor showing higher values than that with BSIs for 2020 (Figure 5B), both of them still followed the bimodal seasonality distribution similar to the normal time-series characteristics. Specifically, in Phase 1, the intensity of NPIs responding to the sudden COVID-19 outbreak in Xi'an effectively met the strict requirements of governments which caused the reported number of reported HFMD cases to decline to near 0 (Figure 5A). In contrast, the predicted value gradually increased to a peak at the transitory stage between Phase 1 and Phase 2 which is also recognized as the main peak of HFMD incidence in previous years. As BSI covariates already contain the effect of policy-related human factors, we adopted the simulated result with meteorological factors as the only predictor to calculate the absolute and relative difference between the predicted and observed values. Table 1 shows a mean cumulative reduction of more than 4837 in Phase 1. In Phase 2, there was a steep rise in the observed number of HFMD cases while the predicted number reached the secondary peak slightly lower than that of the observed with a small relative increase (0.07). The relative reduction in Phase 3 (0.61) was lower than Phase 1 (0.95) despite a low-incidence period at the early time (Figure 5A).

Concerning the analysis for the three clustered classes and three age groups, Figure 6 shows the model results and their cumulative difference compared to the observed value in Table 1. It indicates that the seasonal trends of the predicted number of
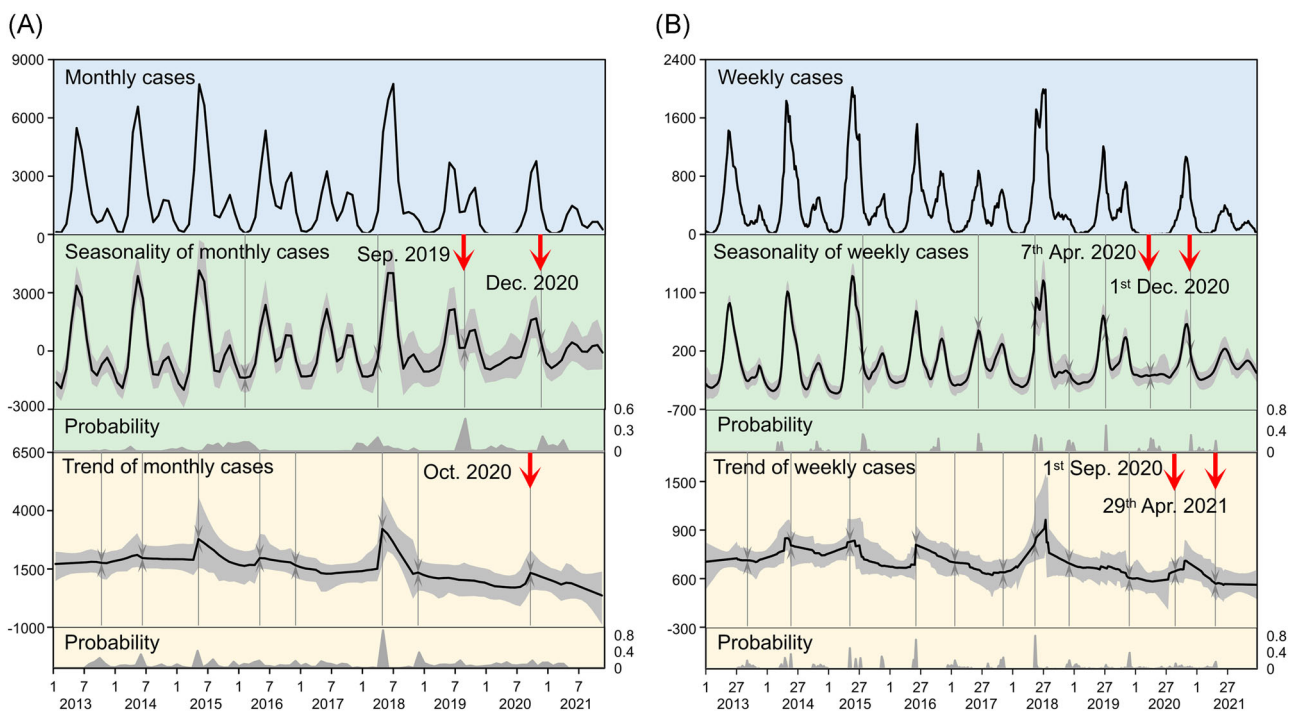

FIGURE 4 Seasonality, trend, and change-points of HFMD in (A) monthly and (B) weekly time series. The seasonality and trend series show the best-fit components with the gray 95% credible interval. The probability parts show the probability of detecting change-points at any given time. HFMD, hand, foot, and mouth disease.
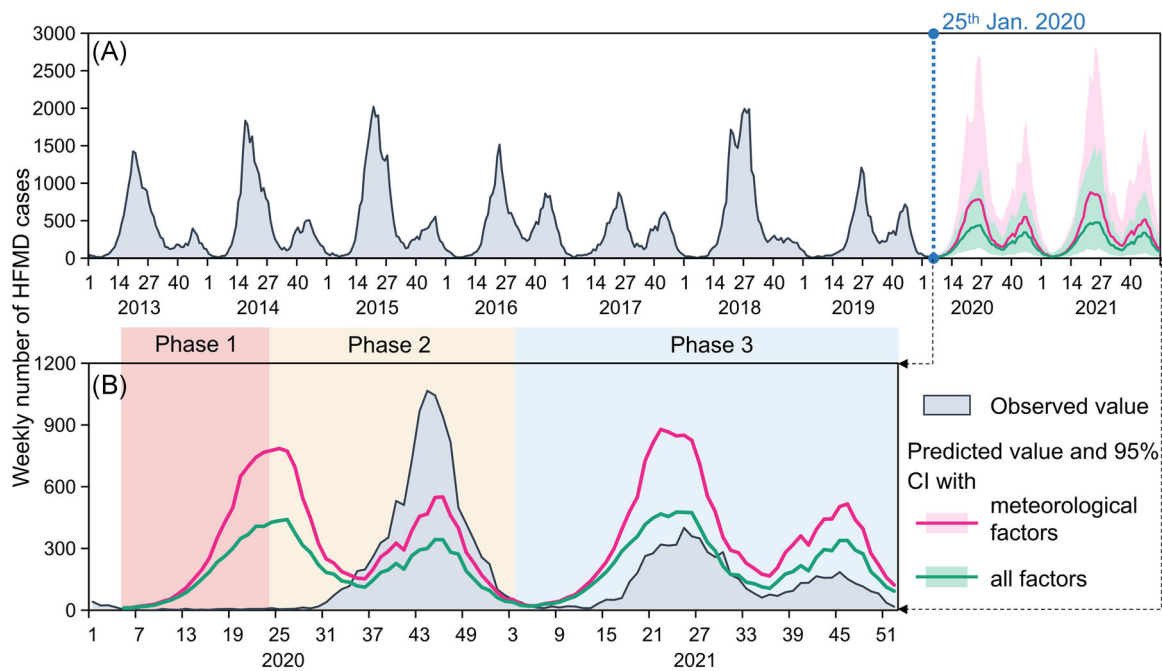
FIGURE 5 The comparison of observed number of HFMD cases with predicted number after the COVID-19 pandemic in Xi'an. (A) The overall predicted result with meteorological factors and BSI covariates based on the HFMD cases of 2013–2019. (B) The observed and predicted weekly number of HFMD cases in three prediction phases. HFMD, hand, foot, and mouth disease.

HFMD cases in the six time-series are similar and the differences in reductions may be due to the distinct ranges of variation in the observed number. For instance, the actual number of HFMD cases for counties of Class 1 dramatically increased in Phase 2 and hence presents a positive mean relative difference compared to Class 2 and Class 3. In addition, the mean relative difference between the observed and predicted number of HFMD cases for the 0–3 years age group was negative in Phase 2 ranging from −0.73 to 4.13 with a mean of −0.08, whereas the changes for the other two high-age groups showed relative growth (Table 1). This inconsistency may be attributed to children younger than 3-year-old occupying the greatest proportion of the total HFMD cases in Xi'an.[22]

Table 2 indicates the results derived from ITSA to distinguish the impacts of governmental NPIs in three temporal periods by calculating the reported level and slope changes at three corresponding interrupted points. Among the posterior probability estimates, the slope change in the long-term trend after Phase 1 poses the strongest effects on HFMD incidence (inclusion probability = 0.55) with a negative β_5 coefficient. This suggests that the trend in HFMD incidence after the 5th week in 2020 decreased significantly compared to the previous trend. Another relevant variate is the level change at the beginning of Phase 1 (inclusion probability = 0.52), and its negative β_2 coefficient further confirmed the immediate level drop of HFMD incidence after the implementation of emergency measures in Xi'an. Results in Table 2 also clearly indicate that the association of NPIs and HFMD incidence gradually diminished in both Phases 2 and 3.

4 | DISCUSSION

As an interdisciplinary study, the present research was designed to investigate how HFMD transmission changes during the COVID-19 pandemic period in Xi'an and quantitatively evaluate the impacts of local governmental NPIs on HFMD incidence. Foremost, the results revealed that the impact of anti-COVID-19 NPIs on HFMD incidence varied between different age groups and spatial locations. Since the pandemic prevention and control have become routine, the risk of infection for young children under 3 years old was lower than for other age groups, whereas preschoolers between 3 and 6 years old and people older than 6 that needed to attend school or work were exposed to a higher risk of infection after resuming classes and production. This phenomenon can be attributed to the difference in behavioral and health monitoring between adults and children, but the deviation caused by their proportions of the total HFMD cases cannot be neglected. In addition, we also explored the associations between HFMD incidence and its relevant factors for three classes of counties. The results revealed that factors related to socioeconomic development exert a stronger influence on HFMD incidence in counties of Class 3, whereas explaining the exact effect mechanism beyond linear correlation is still a challenging task. However, to address this question, more attention should be focused on the differences caused by regional policies and community management that influence epidemic prevention and control. The spatial heterogeneity and inconsistency of HFMD incidence for the 13 counties in Xi'an may be a consequence of the distinct NPIs proposed and implemented for each county. Moreover, the rezoning of the areas on

TABLE 1 Cumulative differences between the observed and simulated weekly number of HFMD cases in three prediction phases for 2020−−2021.

Changes	Phase 1		Phase 2		Phase 3	
	Absolute difference	Relative difference	Absolute difference	Relative difference	Absolute difference	Relative difference
All	−4837.93 (−13199.84, −878.60)	−0.95 (−0.98, −0.82)	749.21 (−22991.22, 10083.85)	0.07 (−0.66, 5.23)	−10603.71 (−44395.60, 3929.08)	−0.61 (−0.87, 1.13)
County						
Class 1	−1630.61 (−1702.50, −1019.34)	−0.94 (−0.98, −0.58)	1712.76 (−1535.33, 27038.89)	0.52 (−0.46, 8.16)	−3709.97 (−4965.12, 4821.81)	−0.67 (−0.90, 0.87)
Class 2	−1730.57 (−5108.96, −230.95)	−0.95 (−0.98, −0.72)	313.35 (−6891.95, 3913.71)	0.09 (−0.63, 6.88)	−4012.55 (−16701.94, 1267.18)	−0.67 (−0.90, 1.41)
Class 3	−2000.73 (−6008.54, −304.26)	−0.96 (−0.99, −0.79)	−816.35 (−9493.98, 2950.23)	−0.19 (−0.73, 3.82)	−5098.58 (−21979.57, 1443.08)	−0.71 (−0.91, 1.36)
Age						
0–3	−2598.75 (−8168.49, −322.75)	−0.93 (−0.97, −0.65)	−520.53 (−15084.14, 4651)	−0.08 (−0.73, 4.13)	−6973.95 (−30693.39, 2514.38)	−0.67 (−0.90, 1.52)
3–6	−2357.70 (−6464.06, −395.43)	−0.98 (−0.99, −0.66)	348.80 (−8239.40, 4177.95)	0.08 (−0.63, 5.65)	−4314.74 (−18768.17, 2033.81)	−0.62 (−0.87, 1.82)
>6	−364.42 (−1113.35, −9.84)	−0.94 (−0.98, −0.15)	655.78 (−852.57,A 1395.23)	0.89 (−0.38, 14.39)	−520.43 (−3517.32, 684.65)	−0.40 (−0.82, 8.18)

Abbreviation: HFMD, hand, foot, and mouth disease.

the north side of the Weihe River as the new Weibei Industrial Zone (consisting of Gaoling, Yanliang, and Lintong counties and defined as Class 1 in this study; http://xadrc.xa.gov.cn/), must have an impact on the social structure of the local community. When it came to the later stage of the COVID-19 pandemic, the industrial areas were highly encouraged to resume production which could have increased both the intra-urban mobility to some extent as well as the healthcare-seeking behaviors of patients with only mild symptoms of HFMD.[30]

Another significant finding in this study is that the responsive NPIs indeed affected the HFMD incidence at different stages with potential long-term impact, which resulted in the transition of HFMD epidemic patterns from 2020 to 2021 in Xi'an. In the first half of 2020, HFMD incidence in Xi'an remained unchanged at a low level due to the early-adopted rigorous NPIs measures, whereas the strict policies were gradually replaced by normalization of epidemic prevention and control as the COVID-19 pandemic eased. During the secondary peak of HFMD incidence in Xi'an (October–November 2020), there emerged an unexpected rise in the number of reported HFMD cases which exceeded the average level over the same period in previous years. The reasons for this result include but are not restricted to the reviving of the tourism and leisure industry, catering services, and entertainment business in Xi'an from the economic depression caused by the COVID-19 pandemic, as well as the sharp increase of outdoor activities and trips after canceling restrictions, which would largely give rise to more frequent contact with patients with HFMD and virus-carrying objects.[31] In addition, we found that in 2021 the seasonality of HFMD incidence in Xi'an steadily returned to the bimodal temporal variation similar to that in 2013–2019, and the predicted HFMD incidence showed seasonal changes consistent with the observed times-series value except for the hysteretic peak possibly owing to the strict interventions reappearing in Xi'an at the beginning of 2021 (i.e., closing schools for winter vacation). At the individual level, the decline in the number of HFMD cases in 2021 had a proven positive influence on more careful personal health management-related conditions such as gastrointestinal infectious diseases. This can also be confirmed by the ITSA results showing that the NPIs performed in Phase 1 only had a short-term direct impact on HFMD incidence in Xi'an, while the potential long-term impact of NPIs was dependent upon the changes in health awareness and hygiene practices of the general public—rather than merely the emergency lockdown demanded in 2020. In the postpandemic era, people consciously comply with the protocols of maintaining personal hygiene, keeping social distance, washing hands, wearing masks, applying health QR codes, and testing nucleic acid, as an indispensable practice in their daily life. The potential long-term impact is mostly reflected in the health consciousness of individuals and their risk assessment, which in turn pervades the thoughts and behaviors of residents.[32]

Furthermore, the study also identified the characteristic tendency of how patients with HFMD select the most suitable medical institutions for healthcare service and help. Serious attention should be given to the evident changes in the proportion of HFMD incidence reported by the maternal and child healthcare hospital as well as
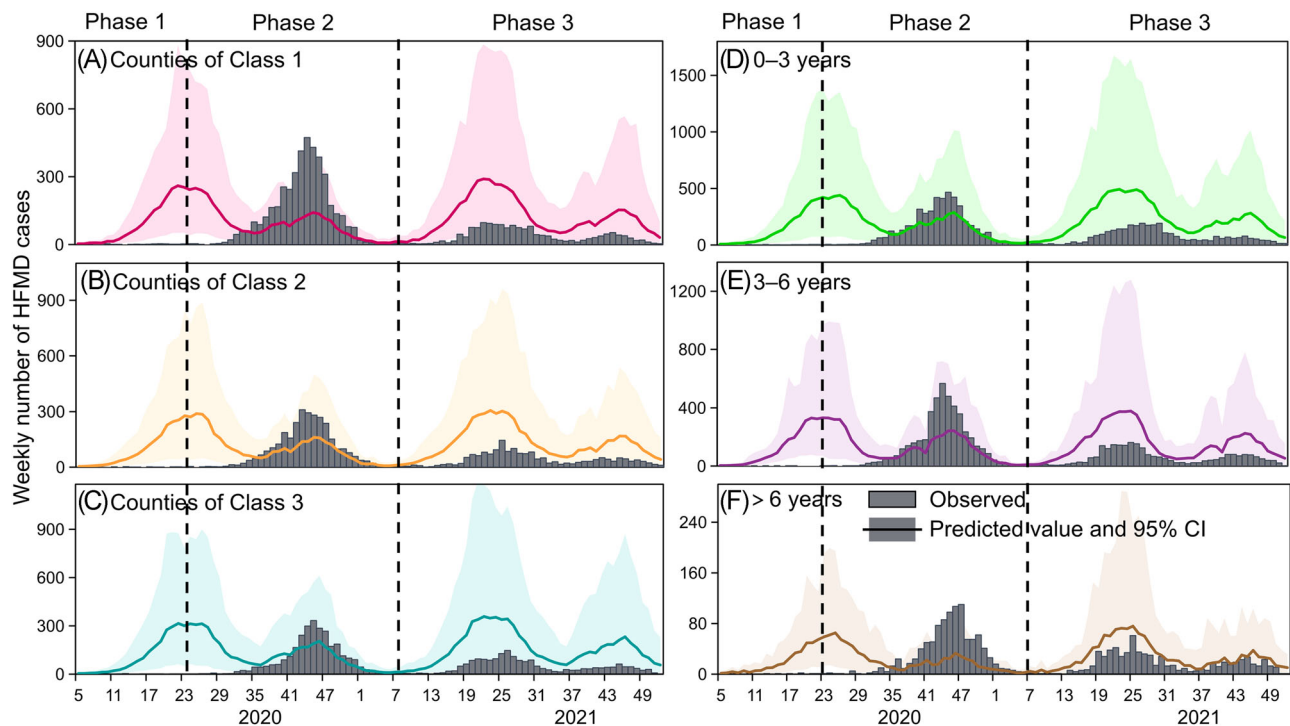
FIGURE 6 The observed and simulated weekly number of HFMD cases in counties of (A) Class 1, (B) Class 2, (C) Class 3, as well as age groups for (D) 0–3 years, (E) 3–6 years, and (F) >6 years in three prediction phases (5th week to 23rd week of 2020; 24th week of 2020 to 3rd week of 2021; 4th week to 52nd week of 2021).

| | Coefficients (10^{-5}) | | | Standardized | Inclusion |
	Mean	2.5%	97.5%	coefficients (10^{-5})	probability
β_1	−16.33	−26.15	−6.51	−4.53	0.01
β_2	−115,913.55	−117,559.22	−114,267.87	−90.78	0.52
β_3	22,882.59	18,262.25	27,502.93	15.24	0.09
β_4	10,966.55	3,148.72	18,784.38	3.71	0.02
β_5	−369.81	−373.91	−365.68	−115.69	0.55
β_6	212.30	182.38	242.22	57.82	0.11
β_7	−47.79	−66.82	−28.75	−6.84	0.03

TABLE 2 Statistics of the regression coefficients of variables in interrupted time series analysis.

hospitals for infectious diseases. The former hospital usually accepts infant patients with HFMD as determined by the number of newborns delivered there. The reduction of HFMD cases reported by hospitals for infectious diseases is mainly attributed to the intense control of infectious diseases during the COVID-19 pandemic. From the perspective of pathogens, as shown in the results, there appears a prominent alternation in the dominant serotype and impacts of virus circulation periodicities on the infection patterns of HFMD which require further inspection. The different infection patterns of HFMD between CVA16 and other enterovirus-infected patients could be associated with the NPI-specific influence provided to different age groups.[33]

This study not only addressed some research gaps identified in existing literature but also presents several limitations and

opportunities for further epidemic disease monitoring and evaluation from both scientific and practical perspectives. First, since detailed vaccination and immunization information acts as critical evidence to support prevalence change analysis,[2] a further in-depth research is accordingly restricted by the deficiency of these data in patients with HFMD in Xi'an. Second, although seasonal and autoregressive components have been considered in the BSTS model, the results of ITSA can be further improved by incorporating more time variables via controlling time-varying confounders and traversal in time points for the possible maximum impact. Finally, uncertainties and complexities rising from the pandemic itself require additional direct evidence linking personal behaviors during the COVID-19 pandemic and the infection risk of HFMD using continual field investigation and questionnaire surveys.

Notwithstanding these limitations, this study provides a preliminary effort in revealing how NPIs specific to COVID-19 acted on the changes of HFMD incidence in Xi'an, which can be extended to other national and international large cities as a reference in synergistic prevention and control of multiple epidemic diseases. Simultaneously, results obtained in this study can also serve as supporting information to link policy-makers with the academic community in reducing diseases and promoting public health.

5 | CONCLUSION

This study quantitatively assessed the positive impacts of NPIs on the reduction of HFMD incidence during the COVID-19 pandemic in Xi'an, of which spatial-temporal characteristics varied in different age groups, geographical locations, and periods (including short- and long-term changes). These findings complement earlier studies on the seasonality dynamics and variation characteristics of HFMD under different affected circumstances and lay the groundwork for future research into the influence of NPIs. Therefore, both direct and indirect NPIs should be developed as targeted public health interventions while improving surveillance strategies for infectious diseases such as HFMD during epidemic trends.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy restrictions.

ETHICS STATEMENT

In China, the collection of data from HFMD cases is part of routine public health surveillance, and such data collection is exempt from institutional review board assessment. Ethical approval for this study was not required in accordance with local legislation and national guidelines.

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