Impact of the coronavirus disease 2019 interventions on the incidence of hand, foot, and mouth disease in mainland China

Zheng Zhao,[a,#] Canjun Zheng,[b,#] Hongchao Qi,[c] Yue Chen,[d] Michael P. Ward,[e] Fengfeng Liu,[b] Jie Hong,[a] Qing Su,[a] Jiaqi Huang,[a] Xi Chen,[a] Jiaxu Le,[a] Xiuliang Liu,[a] Minrui Ren,[b] Jianbo Ba,[f] Zhijie Zhang,[a] Zhaorui Chang,[b]* and Zhongjie Li,[b,g]*

[a]Department of Epidemiology and Health Statistics, Fudan University, Shanghai, China
[b]Division of Infectious Disease, Key Laboratory of Surveillance and Early-warning on Infectious Disease, Chinese Center for Disease Control and Prevention, Beijing, China
[c]Department of Biostatistics, Erasmus University Medical Center, The Netherlands
[d]Department of Epidemiology and Community Medicine, Faculty of Medicine, University of Ottawa, 451 Smyth Rd, Ottawa, ON, Canada
[e]Sydney School of Veterinary Science, The University of Sydney, Camden NSW, Australia
[f]Naval Medical Center of PLA, 880 Xiangyin Road, Yangpu District, Shanghai, China
[g]National Health Commission of China

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Summary

Background In early 2020, non-pharmaceutical interventions (NPIs) were implemented in China to reduce and contain the coronavirus disease 2019 (COVID-19) transmission. These NPIs might have also reduced the incidence of hand, foot, and mouth disease (HFMD).

Methods The weekly numbers of HFMD cases and meteorological factors in 31 provincial capital cities and municipalities in mainland China were obtained from Chinese Center for Disease Control and Prevention (CCDC) and National Meteorological Information Center of China from 2016 to 2020. The NPI data were collected from local CDCs. The incidence rate ratios (IRRs) were calculated for the entire year of 2020, and for January−July 2020 and August −December 2020. The expected case numbers were estimated using seasonal autoregressive integrated moving average models. The relationships between kindergarten closures and incidence of HFMD were quantified using a generalized additive model. The estimated associations from all cities were pooled using a multivariate meta-regression model.

Findings Stringent NPIs were widely implemented for COVID-19 control from January to July 2020, and the IRRs for HFMD were less than 1 in all 31 cities, and less than 0·1 for 23 cities. Overall, the proportion of HFMD cases reduced by 52·9% (95% CI: 49·3−55·5%) after the implementation of kindergarten closures in 2020, and this effect was generally consistent across subgroups.

Interpretation The decrease in HFMD incidence was strongly associated with the NPIs for COVID-19. HFMD epidemic peaks were either absent or delayed, and the final epidemic size was reduced. Kindergarten closure is an intervention to prevent HFMD outbreaks.

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*Corresponding authors.
E-mail address: epistat@gmail.com (Z. Zhang).
[#] These authors contributed equally to this work.

Research in context

Evidence before this study

The containment strategy of integrated nonpharmaceutical interventions (NPIs) was implemented across China to contain the COVID-19 outbreak early in 2020. These NPIs helped control the source of infection, prevented transmission and protected susceptible people; they might have also had an important effect on other communicable diseases such as hand, foot and mouth disease (HFMD) in addition to COVID-19. HFMD is a common childhood illness caused by several enteroviruses, resulting in a substantial burden in China. On Nov 20, 2021 we searched PubMed and preprint archives for articles published with no language or time restrictions, using the terms "HFMD", "COVID-19", "SARS-CoV-2" "interventions", "NPIs" and "control measure". Only two studies were found, which were based on the method of mathematical model using local region's data. Therefore, the effect of these interventions on HFMD in mainland China remains unknown, and the evidence from the real-world study is still lacking.

Added value of this study

To our knowledge, this is the first study to analyze and quantify the impact of COVID-19-related NPIs on HFMD based on data which covered all provinces and municipalities of mainland China between January 1st, 2016 and December 31st, 2020. Our findings showed that the number of HFMD cases in 2020 decreased significantly, the epidemic peak during spring and summer disappeared nationwide and the autumnal peak in South China was delayed. Overall, 260 thousand HFMD cases were prevented in the entire year of 2020. There was a 52·9% (95% CI: 49·3−55·5%) reduction in HFMD cases due to closing kindergartens in 2020, or a total of 255,838 (95% CI: 238,860−268,083) HFMD cases were prevented. The association between kindergarten closure and reduced HFMD incidence varied among cities.

Implications of all the available evidence

The NPIs to control COVID-19 significantly contributed to the containment of HFMD transmission. Closing kindergartens, if necessary, is a feasible intervention to prevent HFMD outbreaks.

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which is the virus that causes coronavirus disease 2019 (COVID-19), is highly infectious. To date, more than 185 million people have been infected and 4 million have died; this pandemic had severe negative impacts on the global economy and caused an economic loss of more than 1 trillion US dollars. In the absence of readily available, effective pharmaceutical agents against this emerging disease during the earlier stages of the pandemic, local governments implemented non-pharmaceutical interventions (NPIs) to slow SARS-CoV-2 transmission and contain the COVID-19 outbreak to manageable levels. These NPIs included the isolation of patients with confirmed infection, contact tracing, quarantine of those potentially exposed to the virus, travel restrictions, school and workplace closure, and cancelation of mass gatherings.[1]

The implementation of the abovementioned NPIs resulted in a rapid decline in the number of new COVID-19 cases across China, albeit at high economic and social costs.[2-4] Coincidently, previous studies have also shown a reduction in the prevalence of several other infectious diseases, such as influenza and dengue, during the period when various NPIs were implemented to control COVID-19.[5-7]

Hand, foot, and mouth disease (HFMD) is a widespread infectious disease mainly affecting children.[8] HFMD has been prevalent in China since at least 2007[9] and was officially included in the national statutory class C infectious disease surveillance program in May 2008.[10] Nationally, HFMD shows semiannual peaks of activity, including a major peak in the spring and early summer followed by a smaller peak in autumn.[11] The current epidemic situation of HFMD remains severe, with a persistently high and increasing incidence rate, causing a substantial disease burden. According to the official reports from the Chinese Center for Disease Control and Prevention (CCDC), the average annual number of cases of HFMD in China has exceeded 2·2 million in the past 10 years, showing the characteristics of a 2-year high−low epidemic cycle; 2020 was expected to be a high-incidence year had the COVID-19 outbreak not occurred.

COVID-19-related NPIs provided a unique opportunity to observe the real-world effectiveness of NPIs in mitigating HFMD transmission using this natural experiment with a comparative study design. In this study, we aimed to analyze and quantify the effect of NPIs on the incidence of HFMD in mainland China in 2020.

Methods

Study area and HFMD case data

This study included 31 provincial capitals and municipalities in China. CCDC provided the individual case-based HFMD surveillance data, with personal identification (e.g., patient names) removed, from the Chinese infectious diseases surveillance system for the period between January 1, 2016, and December 31, 2020. The data included sex, date of birth, date of symptom onset, and clinical type. The cases were either clinically diagnosed or laboratory confirmed, and the case definition has been described previously.[11] The weekly numbers of HFMD based on the date of symptom onset were aggregated at the city level and then categorized into different subgroups according to sex (male or female), age (0−4 years, 5−14 years, or ≥15 years), and clinical type (mild or severe).

NPI data

According to the documents issued by the local governments based on the Joint Prevention and Control Mechanism about COVID-19, 31 local CDCs collected the start and end dates of kindergarten closure as well as primary and secondary school closures; restricted population movement; lockdown of districts and other public places; and the timing of first-level to third-level public health emergency responses in the provincial capitals in mainland China. A matrix of Cramér's V coefficient was used to examine the associations among the NPIs.

Meteorological data

Daily meteorological data, including mean temperature, mean relative humidity, mean wind speed, and sunshine hours, were obtained from the National Meteorological Information Center of China. Each meteorological variable was incorporated into the weekly data. A matrix of Spearman correlation coefficients was used to examine the associations among meteorological factors and select representative variables to avoid multicollinearity.

Statistical analysis

Analysis of the impact of COVID-19-related NPIs on HFMD incidence in 31 provincial capitals in mainland China. Based on the weekly onset number of HFMD cases, we fit 31 city-specific autoregressive integrated moving average (ARIMA) models for the pre-COVID-19 period (2016−2019) and used these models to predict the incidence rate of HFMD in 2020. We compared the expected and observed case counts in 2020 and calculated the incidence rate ratios (IRRs) as the sum of the observed cases divided by the sum of the expected cases estimated from the ARIMA models. Since the NPIs were essentially discontinued in all regions in China, we also calculated the separate IRRs for weeks 1−31 (earlier stage) and weeks 32−52 (later stage) of 2020. Concomitantly, we subtracted the sum of the observed cases from the sum of the expected value as the number of city-specific prevented HFMD cases in the three periods mentioned above and added the numbers for the 31 cities.

Since HFMD has strong seasonality, a seasonal ARIMA model (p,d,q) (P,D,Q)s was used for modeling, where p and P are autoregressive order and seasonal autoregressive order respectively, and q and Q are the moving average and seasonal moving average respectively. d and D are the difference order and seasonal difference order respectively, and s is the seasonal period.

Seasonal ARIMA models were fitted and utilized based on the following four procedures:[12] (1) Sequence stability: Time series diagrams from the 1st week of 2016 to the 52nd week of 2019 were generated for each of the 31 cities. The sequences of the weekly onset of HFMD cases were transformed into stable sequences; (2) Model recognition and parameter estimation: The order was determined through the time series of the autocorrelation function (ACF) and partial autocorrelation function (PACF), and possible models were selected for further analysis. The least squares method was used to estimate the model parameters and verify whether the unknown parameters were significant; (3) Model diagnostics: The Ljung-Box white noise test was performed on the residual sequence of the observed values and the fitted values to exclude non-white noise of the residual values. The optimal model was determined based on the Akaike information criterion (AIC) value; and (4) Model prediction: The constructed seasonal ARIMA model for each city was used to predict the number of weekly HFMD cases in each city in 2020 (weeks 1−52), assuming that there was no COVID-19 outbreak and associated NPIs.

A sensitivity analysis was conducted separately with a random forest machine learning approach.

Quantification of the effect of COVID-19-related NPIs on the incidence of HFMD. In the first stage, a generalized additive model (GAM) was applied to determine the city-specific associations between NPIs and weekly cases of HFMD during the study period. The distribution of HFMD cases was assumed to follow a negative binomial distribution, considering that the variances of the weekly counts were larger than their means. The meteorological factors were incorporated into the model in the form of splines, and the seasonality of HFMD was controlled by cyclic cubic spline curves; time splines were also considered to control for the time trend of HFMD incidence, and the optimum degrees of freedom were determined based on the quasi-AIC. The GAM was calculated as follows:

$$\mathrm{Log}(E(y_t)) = \beta_0 + as.factor(NPI) + s(weather, df) + s\left(week,\ bs{=}''cc'', df\right) + s(t, df)$$

where y_t is the weekly count of HFMD at time t; β_0 is the intercept; *NPI* and *weather* are the NPI and meteorological data; *week* is the week of a year, ranging from 1 to 52; *t* is the time, ranging from 1 to 260.

In the second stage, a multivariate meta-regression model was used to obtain the national-average associations between NPIs and HFMD by pooling the

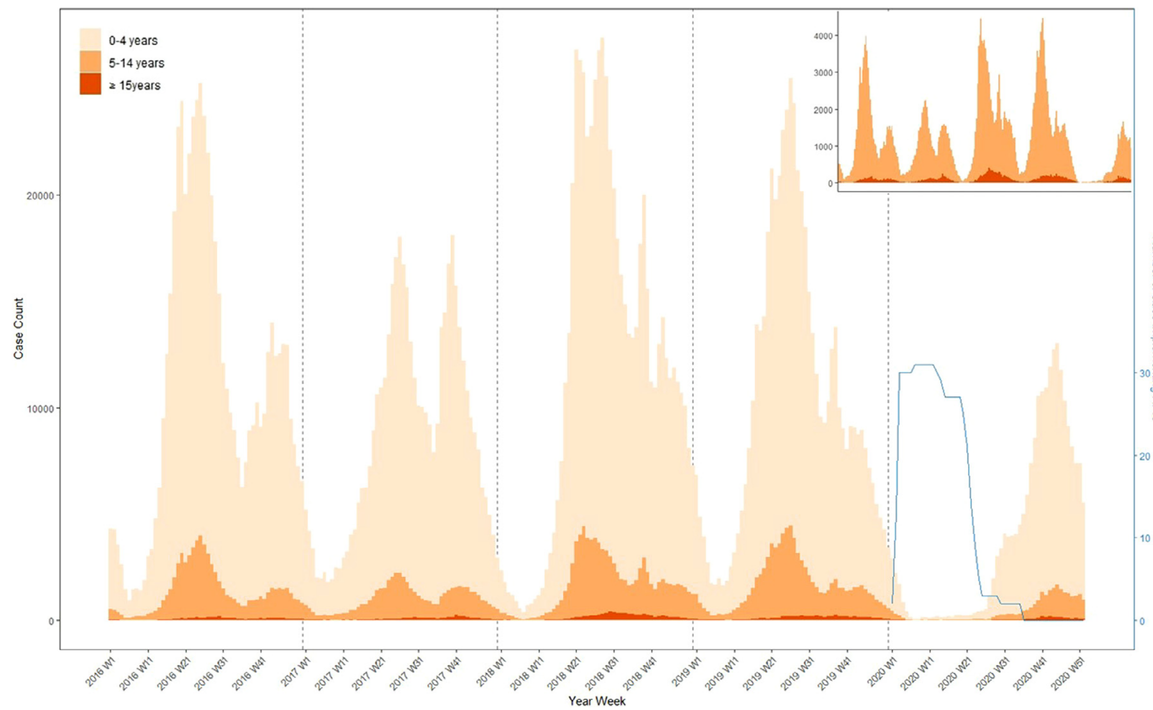

Figure 1. Number of cases of hand, foot, and mouth disease stratified by the week of illness onset in 2016–2020. The insert shows the number of cases by week of illness onset in all individuals, excluding those aged 0–4 years. The blue curve shows the number of cities implementing NPIs from the 1st week to the 52nd week of 2020.

association estimates across cities, taking between-city heterogeneity into account, which was tested and quantified using the Cochran's Q test and I^2 statistic. A multivariate meta-regression model derived from the random-effects model formula was expressed as follows:

$$\beta_i = \alpha + b_i + \varepsilon_i$$

where β_i denotes the effect of kindergarten closure in city i in GAM, α denotes the overall mean of the effect, b_i is the city-specific effect for city i, and ε_i is the random error term.

We pooled the estimates of each city to obtain the overall RRs and calculated the percentages and numbers of prevented HFMD cases due to kindergarten closure in 2020.

All analyses were further stratified by sex (male or female), age (0–4 years, 5–14 years, or ≥15 years), and clinical type (mild or severe) to investigate whether these variables modified the association between NPIs and HFMD.

Statistical analyses were performed with *forecast, mgcv*, and *mvmeta* packages in R software (version 3.6.1; R Foundation for Statistical Computing, Vienna, Austria) and ArcGIS software (version 10.0; Environmental Systems Research Institute Inc., Redlands, CA, USA). A P-value of <0·05 was considered significant.

Role of the funding source

The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Results

Descriptive analysis

A total of 2,423,670 HFMD cases were reported in 31 provincial capital cities from 2016 to 2020. Overall, the number of HFMD cases in 2020 was significantly lower than that in the previous 4 years (Figure 1). The majority of the cases still occurred in children aged 5 years and below, and less than 1% of the cases were reported in children aged ≥15 years. Between 2016 and 2019, major peak occurred in spring or early summer, and autumn; in 2020, the former peak disappeared when strict NPIs were widely implemented (weeks 3–20); however, the latter peak rebounded when the NPIs were essentially discontinued in late July 2020 (week 31). The number of cases in these capitals slowly increased from early February to late June (weeks 6–25), with a total count of no more than 500 cases per week. However, it began to increase rapidly after mid-July and reached a peak in the beginning of October (week 40); the

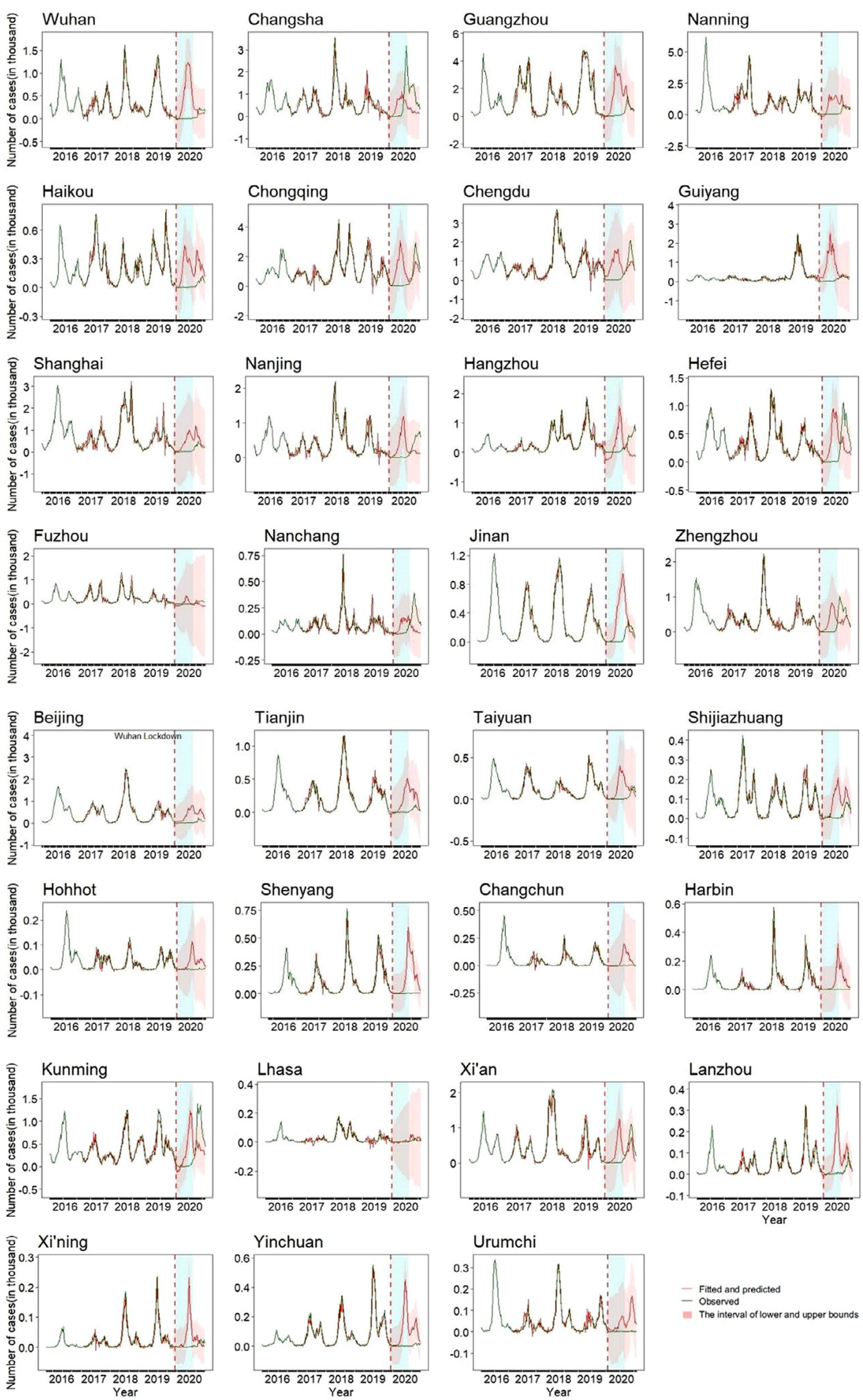

Figure 2. Observed hand, foot, and mouth disease case counts in 31 provincial capitals in mainland China from 2016 to 2020, compared with the fitted (2016−2019) and predicted (2020) case counts obtained using the ARIMA models in the absence of COVID-19 outbreaks and without the implementation of COVID-19-related NPIs. The light-blue shaded part indicates the observed and estimated case counts from early January to the end of July 2020, when NPIs were strictly implemented.

epidemic peak lasted until late November (week 47), and the number of cases declined thereafter. The HFMD epidemic trend showed an obvious inverse relationship with the number of cities that implemented NPIs (Figure 1).

Impact of COVID-19 and NPIs on the incidence of HFMD in 31 provincial capitals in mainland China

Thirty-one city-specific ARIMA models were established (Supplementary Information Table S1 and Figure S1). Before the stringent NPIs were lifted at the end of July 2020, the reported case counts were lower than that the predicted case counts for all 31 cities (Figure 2); all IRR values for that period were less than 1, while that in 23 cities was less than 0·1 (Figure 3b and Supplementary Information Table S2). In the earlier stage, 8,000−10,000 HFMD cases were prevented in the capital cities of East China (Nanjing, Hangzhou, Hefei, Fuzhou, and Nanchang) and Zhengzhou, Changsha, and Xi'an (Figure 4b and Supplementary Information Table S2). Thereafter, the observed HFMD case counts in those cities began to rise sharply and exceeded the predicted case counts (Figure 2); the IRR values in the later stage were higher than 1 (Figure 3c). A similar pattern was observed in Chongqing, Chengdu, and Kunming in Southwest China (Figure 2 and Figure 3c), with more than 20,000 HFMD cases prevented in the earlier stage of 2020 (Figure 4b and Supplementary Information Table S2). In 2020, the number of reported HFMD cases in northern (Beijing, Tianjin, Shijiazhuang, Taiyuan, and Hohhot) and northeast cities (Shenyang, Changchun, and Harbin) were markedly lower than the predicted numbers (Figure 2), and the IRR values for 2020 as well as early and late 2020 were all less than 1 (Figures 3a-c), with 1,000−16,000 HFMD cases prevented throughout the 2020 period (Figure 4a and Supplementary Information Table S2).

In total, 260,000 cases of HFMD were prevented in 2020. The sensitivity analysis using a random forest approach provided similar results (Supplementary Information Table S3 and Figure S2).

Quantitative impact of COVID-19 and NPIs on the incidence of HFMD

The Cramér's V coefficient matrix showed strong correlations among the five NPIs assessed, and the *P*-value for all correlation coefficients was less than 0·01. Only kindergarten closure was chosen as a significantly important variable and was retained in the analysis (Supplementary Information Table S4). The Spearman correlation coefficients of mean temperature with mean relative humidity, mean wind speed, and sunshine hours were 0·83, 0·72, and 0·08, respectively, which were all significant, and the mean temperature was finally chosen in the model (Supplementary Information Table S5).[13]

The impact of kindergarten closure on HFMD incidence in 2020 varied among different cities (Figure 5), showing obvious spatial heterogeneity (I^2= 92·4%, P<0·0001, Supplementary Information Table S6). In 11 out of 31 cities, kindergarten closure was associated with a 50% reduction in HFMD incidence (Figure 5). This effect was generally similar across the subgroups (Supplementary Information Figures S3a-g). Overall, 52·9% (95% CI: 49·3%−55·5%) or 255,838 (95% CI: 238,860−268,083) HFMD cases were prevented by

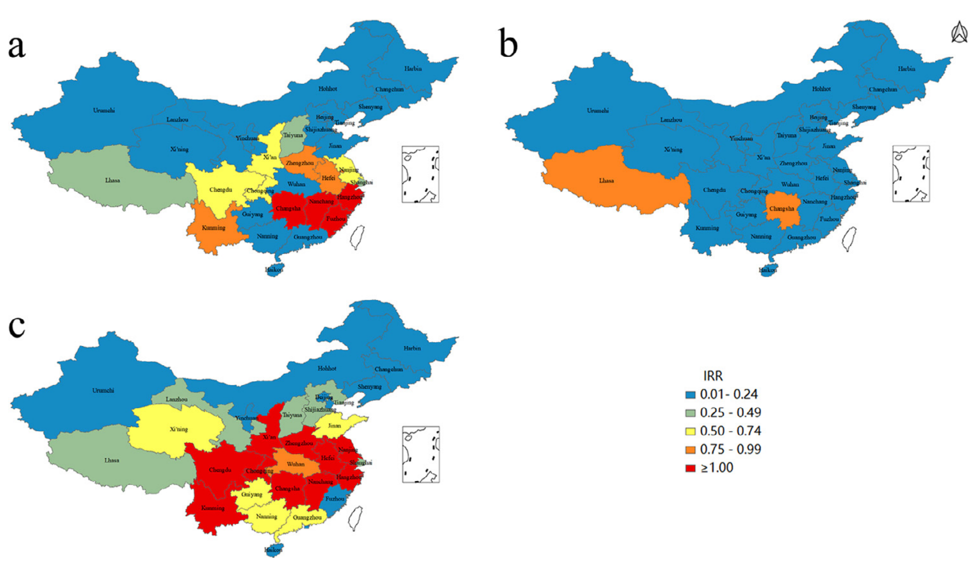

Figure 3. IRR (total observed hand, foot, and mouth disease case number divided by the total expected case number) in 31 provincial capitals in mainland China for (a) the entire 2020, (b) early January to the end of July, and (c) early August to the end of December from blue (low) to red (high)

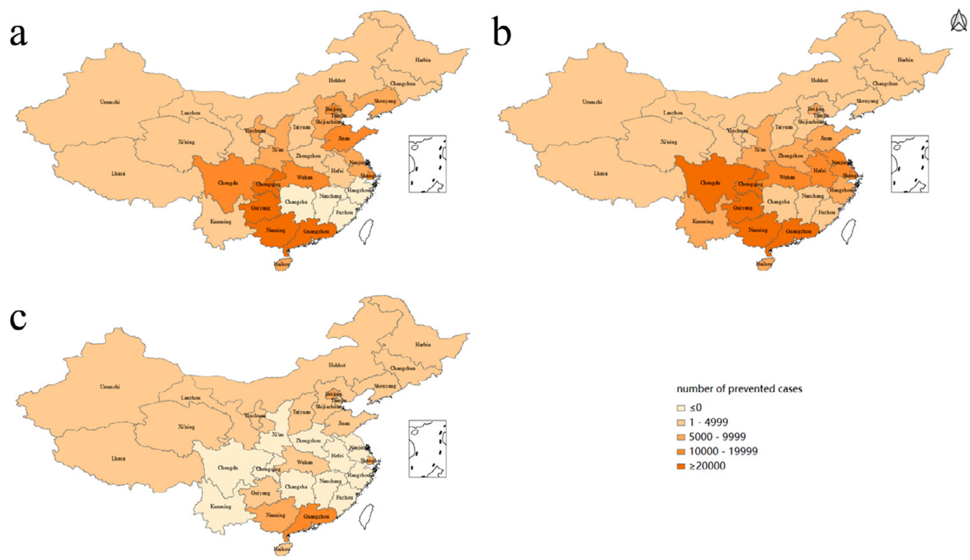

Figure 4. Number of cases of hand, foot, and mouth disease prevented in 31 provincial capitals in mainland China for (a) the entire year of 2020, (b) early January to the end of July, and (c) early August to the end of December.

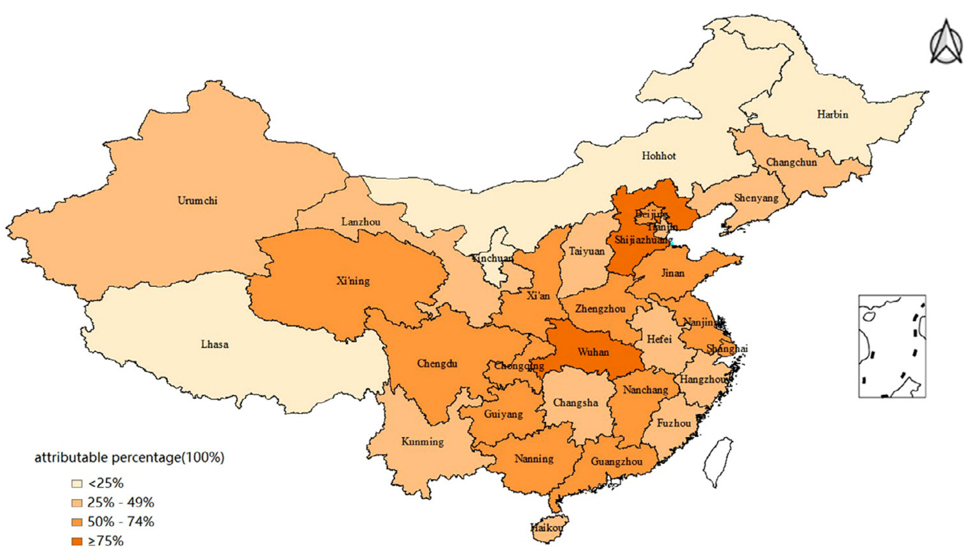

Figure 5. Percentage of hand, foot, and mouth disease cases prevented by kindergarten closure in 31 provincial capitals in mainland China in 2020.

kindergarten closure in 2020; the implementation of this NPI decreased the occurrence of mild HFMD cases, HFMD in those less than 5 years of age, or HFMD in boys (Table 1).

Discussion

Our study showed a substantial decrease in the number of reported HFMD cases in 2020, the year after SARS-CoV-2 was confirmed and NPIs were widely implemented to prevent its transmission. The decrease in HFMD incidence was strongly associated with the implementation and timing of NPIs in all 31 provincial capital cities. These data provide clear evidence that the adoption of NPIs can effectively mitigate the transmission of HFMD.

The epidemic characteristics and peak of HFMD also changed due to the implementation of strict NPIs. In the provincial capital cities of North and Northeast China, which only had one epidemic peak in spring or summer in 2016–2019, the counterfactual predicted values for 2020 were consistently higher than those reported, and this epidemic peak disappeared in 2020. The same phenomenon was observed in Southern China in the first half of 2020. In the latter half of 2020, when strict NPIs were discontinued, obvious

Strata	Attributable number	95% CI	Attributable percentage (100%)	95% CI
Overall	255,838	(238,860−268,083)	52·9	(49·3−55·5)
Clinical Type				
Mild	252,325	(235,160−264,769)	53·2	(49·7−55·8)
Severe	339	(151, 454)	36·4	(16·2−48·7)
Sex				
Male	154,413	(146,512−160,203)	54·6	(51·8−56·6)
Female	109,559	(102,521−114,665)	53·3	(49·9−55·8)
Age (year)				
0−4	208,329	(183,588−223,148)	53·0	(46·7−56·8)
5−14	34,511	(33,390−35,324)	57·1	(55·2−58·4)
≥15	2,876	(2,516−3,140)	47·2	(41·2−51·5)

***Table 1*: Pooled numbers and percentages of hand, foot, and mouth disease cases prevented by kindergarten closure in 31 provincial capitals of mainland China in 2020.**

rebounds of HFMD occurred mostly in the southern cities, which had a secondary epidemic peak in autumn before the outbreak of COVID-19 and the implementation of related NPIs. The autumn peak in HFMD incidence was delayed in 2020. This has an important implication for disease preparedness: NPIs can be used to buy time to enable the population at risk of becoming immune via vaccination in the face of outbreaks.[14]

The causative pathogens of HFMD belong to the enterovirus family[15,16] and can be transmitted through different routes such as close personal contact, contact with contaminated objects and surfaces, and respiratory and fecal-oral routes. Meteorological factors, such as temperature, relative humidity, mean wind speed, and sunshine hours, have been previously reported to influence HFMD transmission as a result of their effects on virus survival.[15,17-19] They were controlled explicitly as covariates, and the impact of other unconsidered factors was implicitly absorbed in the splines of time in the analysis. Among the different NPIs assessed, kindergarten closure was identified as the most important NPI, and the association between kindergarten closure and reduced HFMD incidence varied across the cities included in this study. The results showed an obvious spatial heterogeneity, which may be partly due to the heterogeneity in the role of meteorological conditions, together with different population densities and population movements.[20,21]

Schools and kindergartens represent the most socially dense environment (3−5 m^2/child) when compared with offices (18 m^2/person) or homes (36−44 m^2/person),[22,23] and children aged less than 5 years are at the highest risk of contracting HFMD. Kindergartens are common places for HFMD outbreaks.[24-26] HFMD pathogens can spread easily among children both in and out of classrooms through close contacts via contaminated hands, toiletries, personal products, toys, tableware, and beddings.[27,28] HFMD is highly infectious; some children can transmit the virus before the onset of symptoms, and infected patients can excrete the virus for a long period of time.[29] In a previous outbreak, HFMD rapidly spread across 10 out of 11 classrooms within 11 days before HFMD control measures were implemented.[30]

Kindergarten closure as a COVID-19 intervention measure in 2020 was associated with a 55% reduction in the incidence of HFMD cases. Vaccines against EV-A71 are available in mainland China, which is the only effective means to prevent HFMD, and have protective efficacies of more than 90% against EV-A71-associated HFMD.[31] However, these vaccines do not protect against HFMD caused by CV-A6 or other viruses,[32] and NPIs are still the most important measures to control the incidence of HFMD. In our study, we found that kindergarten closure is an effective measure to prevent the outbreaks of HFMD. In practice, however, closing kindergartens is difficult to implement since it will have certain effects on normal productivity and work life.[33] For example, during periods of kindergarten closure, parents are more likely to take leave due to the need to devote time and effort to caring for their young children.[34] Therefore, the prevention and control measures implemented in kindergartens must be strengthened instead of closing kindergartens, and techniques with higher sensitivities of case detection are needed to handle cases in a timely manner to prevent further spread of the disease during an epidemic.

Closing kindergartens had a similar impact on HFMD incidence for the age groups of 0−4 and 5−14 years, with multicollinearity between the time of primary and secondary school closure and kindergarten closure. Kindergarten closure had a smaller effect on the incidence of severe HFMD than on that of mild HFMD. This is probably because the closure of kindergartens will not greatly change the behavior of seeking care for severe cases due to the severity of illness; hence, it would not make a large difference in this cohort.

In summary, the NPIs adopted for controlling COVID-19 had a major effect on the prevention and control of HFMD. Staying at home reduces the chances of infection and isolates patients with HFMD. Social distancing measures, including closing schools, extending holidays, and canceling mass gatherings and events (such as music festivals, religious gatherings, cultural celebrations, conferences, and political events), decrease the frequency and duration of social contacts among people, thus reducing person-to-person transmission of the viruses causing HFMD.[35,36] Reducing contact frequency and increasing social distance, together with improved personal hygiene (e.g., handwashing and wearing masks), can effectively block the transmission of HFMD, protect vulnerable populations, and mitigate HFMD spread at the community level.[37]

Our study has several limitations. First, as a result of the COVID-19 epidemic, HFMD cases might have been underdiagnosed and underreported in 2020 to a certain degree; however, this cannot be quantified at the moment. Second, the different enterovirus subtypes of HFMD were not considered separately in this study as the impacts of NPIs on various serotypes of HFMD were not taken into account. Third, as the NPIs were more strongly implemented during the COVID-19 pandemic than during the pre-pandemic periods, and because the personal hygiene practices (e.g., hand washing and wearing of face masks) have significantly improved since the onset of the pandemic, the impacts of NPIs on the HFMD incidence were overestimated.

The decrease in HFMD incidence was strongly associated with the implementation of NPIs for COVID-19 control. Because of the wide implementation of NPIs, HFMD epidemic peaks were absent or delayed, and the number of HFMD cases was significantly lower than expected. Kindergarten closure is an effective measure to prevent HFMD outbreaks.

Contributors

Zhijie Zhang and Zhaorui Chang designed and supervised the study. Zheng Zhao, Canjun Zheng and Zhongjie Li finalised the analysis, and interpreted the findings. Fengfeng Liu, Jie Hong and Qing Su assisted in data analysis. Zheng Zhao and Hongchao Qi wrote the drafts of the manuscript. Yue Chen, Michael P. Ward and Jianbo Ba commented on and helped revise drafts of the manuscript. Jiaxu Le, Jie Hong, Qing Su, Jiaqi Huang, Xi Chen and Minrui Ren participated in collection and management of data.

Declaration of interests

We declare that we have no conflicts of interest.

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Availability of data

The datasets used and analyzed during the current study available from the corresponding author on reasonable request.

Editor note

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.lanwpc.2021.100362.

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