Nonpolio Enterovirus Activity during the COVID-19 Pandemic, Taiwan, 2020

Shu-Chen Kuo,[1] Hsiao-Hui Tsou,[1] Hsiao-Yu Wu, Ya-Ting Hsu, Fang-Jing Lee, Shu-Man Shih, Chao A. Hsiung, Wei J. Chen[1]

Author affiliations: National Health Research Institutes, Zhunan, Taiwan

DOI: https://doi.org/10.3201/eid2701.203394

In Taiwan, lower nonpolio enterovirus activity during the coronavirus disease pandemic in 2020 compared with 2014–2019 might be attributable to adherence to nonpharmaceutical interventions. The preventable fraction among unexposed persons indicated that 90% of nonpolio enterovirus activity might have been prevented during 2014–2019 by adopting the same measures enforced in 2020.

Nonpharmaceutical interventions have been shown to be effective in preventing the spread of infectious diseases. The strict compliance with nonpharmaceutical interventions implemented during the coronavirus disease (COVID-19) pandemic has been associated with a decline in influenza activity in many countries, including Taiwan (*1*–*4*). Handwashing, disinfecting frequently touched surfaces, and closure of schools might also be effective against nonpolio enteroviruses (NPEV), which commonly cause a spectrum of illnesses in young populations in Asia (*5*). We observed lower NPEV activity during the 2019–20 season in Taiwan compared with the average of the 5 previous seasons, which might be attributable to strict compliance with nonpharmaceutical interventions. We further estimated the protective effect that could have been achieved if the population strictly adhered to the same nonpharmaceutical interventions during those previous seasons.

We collected nationwide data on weekly outpatient and emergency department (ED) visits during November 2014–June 2020 from the Taiwan National Infectious Disease Statistics System (https://nidss.cdc.gov.tw) (*6*). Patients ≥15 years of age were excluded because of their milder symptoms and low number of cases. The original data were transferred from the National Health Insurance program of Taiwan, which covers >99% of Taiwan residents (Appendix, https://wwwnc.cdc.gov/EID/article/27/1/20-3394-App1.pdf). The Institutional Review Board of the National Health Research Institutes approved this study (approval no. EC1051207-R4).

NPEV activity was measured by using the number of visits that yielded diagnoses of hand, foot, and mouth disease (International Classification of Diseases [ICD], 9th Revision, Clinical Modification, code 074.3 or ICD, 10th Revision, Clinical Modification, code B08.4) or herpangina (ICD, 9th Revision, Clinical Modification, code 074.0 or ICD, 10th Revision, code B08.5). The period from week 47 of 1 year and week 23 of the following year was defined as 1 season. We estimated the change in NPEV activity after the first imported COVID-19 case in Taiwan, when nonpharmaceutical interventions were introduced and enforced, by using a difference-in-difference model used in a previous influenza study (Appendix) (*4*). The total number of outpatient and ED visits for NPEV at baseline was adjusted to eliminate the preintervention differences in NPEV activity between groups (2019–20 season vs. 2014–2019 seasons). The total number of outpatient and ED visits for all disease in different weeks and different years was used for normalization because their numbers decreased after the COVID-19 pandemic. We estimated the preventable fraction among the unexposed (PF_u) to measure the reduction of NPEV that would have been possible in each week of the 2014–2019 seasons, had the same nonpharmaceutical interventions been strictly followed, and adjusted PF_u to control for potential confounder (Appendix).

The number of NPEV visits during the 2019–20 season was 81,942, compared with the average of 205,979 during the 2014–2019 seasons (Appendix Table 1). NPEV activity increased after week 16 across the past 6 seasons except 2019–20, when the earlier low level of weekly activity continued (Figure; Appendix Figure 1). The difference-in-difference analysis revealed that after normalization by visits for NPEV at baseline and for all diseases, NPEV activity during weeks 16–23 in the 2019–20 season was significantly lower than during the same calendar weeks of the 2014–2019 seasons (Appendix Table 2). The lower activity during weeks 16–23 in 2019–20 remained significant across all age groups and hospital settings (Appendix Table 3, 4). The weekly PF_u increased from 73% to 90% (from 17% to 71% for adjusted PF_u) during weeks 16–23 (Table; Appendix Table 5). Similar benefits of the nonpharmaceutical interventions were observed across different age groups of patients and hospital settings (Table; Appendix Table 6).

We observed a significant and persistent decrease of NPEV during the 2019–20 season, which might be attributable to strict compliance with the nonpharmaceutical interventions. Up to 90% (71% adjusted) of NPEV activity might have been prevented during the 2014–2019 seasons by adopting the same nonpharmaceutical interventions enforced in 2020. Many

[1]These authors contributed equally to this article.

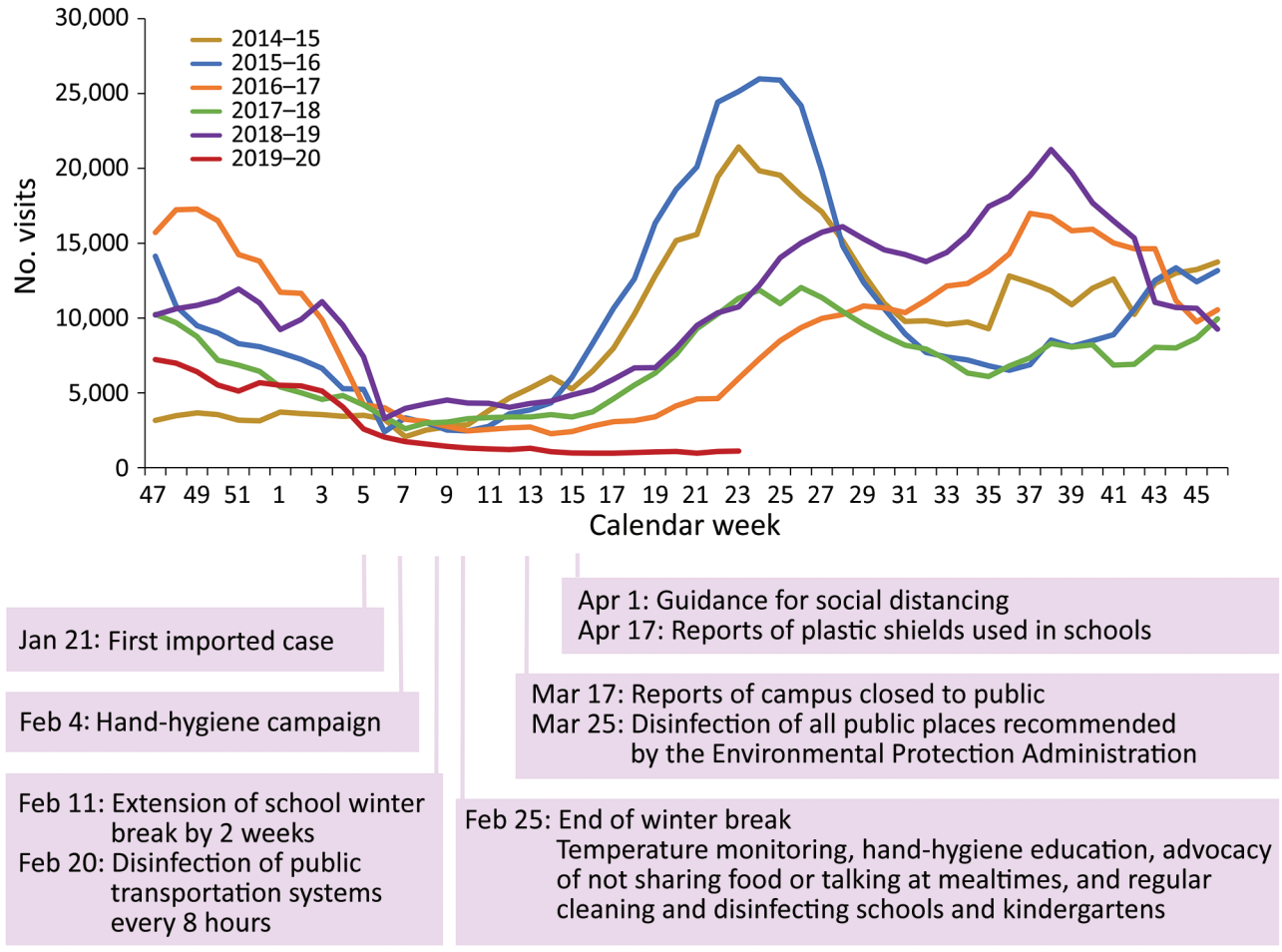


Figure. Nonpolio enterovirus activity during 2019–20 season compared with the same weeks in the previous 5 seasons in patients <15 years of age, Taiwan. The y-axis represents the number of outpatient department and emergency department visits in which a diagnosis of hand, foot and mouth disease or herpangina was made for patients <15 years of age.

factors, such as detection bias and healthcare avoidance, might confound our analyses. However, the detection of NPEV is based on symptoms and was less likely to be affected by the COVID-19 pandemic. In addition, COVID-19 had little impact on the surveillance system in Taiwan because <450 total COVID-19 cases had been reported as of June 17 and no local cases have been reported since April 12.

Our study is limited by the healthcare avoidance caused by the COVID-19 pandemic (4). The normalization procedure using the number of visits for all diseases in our study and subgroup analyses on ED patients (Appendix Table 4, 6) are insufficient to eliminate the impact of healthcare avoidance; active surveillance is required. The effect of individual nonpharmaceutical intervention is difficult to assess. The

Table. Weekly estimated PF_u during calendar weeks 16–23 in 2020 compared with the same weeks in the previous 5 seasons in patients <15 years of age, by age group, Taiwan*

Calendar week	Estimated PF_u (95% CI)				
	Overall	0–2 y	3–4 y	5–9 y	10–14 y
16	0.73 (0.67–0.78)	0.55 (0.46–0.63)	0.76 (0.70–0.81)	0.78 (0.73–0.83)	0.74 (0.68–0.79)
17	0.76 (0.72–0.80)	0.61 (0.54–0.67)	0.79 (0.75–0.82)	0.81 (0.77–0.85)	0.78 (0.73–0.81)
18	0.79 (0.76–0.82)	0.66 (0.61–0.70)	0.82 (0.79–0.84)	0.84 (0.81–0.86)	0.81 (0.78–0.83)
19	0.82 (0.80–0.84)	0.70 (0.67–0.73)	0.84 (0.82–0.86)	0.86 (0.84–0.88)	0.83 (0.81–0.85)
20	0.84 (0.82–0.86)	0.74 (0.71–0.76)	0.86 (0.84–0.88)	0.88 (0.86–0.89)	0.86 (0.84–0.87)
21	0.86 (0.84–0.88)	0.77 (0.74–0.80)	0.88 (0.86–0.89)	0.89 (0.88–0.91)	0.87 (0.86–0.89)
22	0.88 (0.86–0.90)	0.80 (0.77–0.83)	0.89 (0.87–0.91)	0.91 (0.89–0.92)	0.89 (0.87–0.91)
23	0.90 (0.87–0.91)	0.82 (0.79–0.85)	0.91 (0.89–0.93)	0.92 (0.90–0.94)	0.91 (0.88–0.92)

*All values are statistically significant. PF_u, estimated preventable fraction among the unexposed.

prolonged winter break might have played a major role in reducing NPEV activity. However, considering the high contagiousness of NPEV, their activity was expected to peak after school reopening if no other interventions were implemented. The persistent low NPEV activity throughout the semester, which began in March 2020, indicated the effectiveness of other interventions.

Acknowledgments

We thank the Taiwan CDC for making their data publicly available. We also thank Kung-Yee Liang, Huey-Kang Sytwu, Shiow-Ing Wu, and Yu-Chieh Cheng for their valuable comments and support.

This project was supported by intramural grants from the National Health Research Institutes (grant nos. IV-109-PP-01, PH-109-PP-02, and PH-109-GP-02).

About the Author

Dr. Kuo is an attending physician and associate investigator at the National Institute of Infectious Diseases and Vaccinology, National Health Research Institutes, Taiwan. His primary research interest involves infectious diseases and clinical microbiology.

References

1. Kuo SC, Shih SM, Chien LH, Hsiung CA. Collateral benefit of COVID-19 control measures on influenza activity, Taiwan. Emerg Infect Dis. 2020;26:1928–30. https://doi.org/10.3201/eid2608.201192
2. Galvin CJ, Li YJ, Malwade S, Syed-Abdul S. COVID-19 preventive measures showing an unintended decline in infectious diseases in Taiwan. Int J Infect Dis. 2020;98:18–20. https://doi.org/10.1016/j.ijid.2020.06.062
3. Choe YJ, Lee JK. The impact of social distancing on the transmission of influenza virus, South Korea, 2020. Osong Public Health Res Perspect. 2020;11:91–2. https://doi.org/10.24171/j.phrp.2020.11.3.07
4. Sakamoto H, Ishikane M, Ueda P. Seasonal influenza activity during the SARS-CoV-2 outbreak in Japan. JAMA. 2020;323:1969–71. https://doi.org/10.1001/jama.2020.6173
5. Owino CO, Chu JJH. Recent advances on the role of host factors during non-poliovirus enteroviral infections. J Biomed Sci. 2019;26:47. https://doi.org/10.1186/s12929-019-0540-y
6. Jian SW, Chen CM, Lee CY, Liu DP. Real-time surveillance of infectious diseases: Taiwan's experience. Health Secur. 2017;15:144–53. https://doi.org/10.1089/hs.2016.0107

Address for correspondence: Wei J. Chen, Center for Neuropsychiatric Research, National Health Research Institutes, No. 35 Keyan Rd, Zhunan, Miaoli 350, Taiwan; email: wjchen@nhri.edu.tw; or Shu-Chen Kuo, National Institute of Infectious Diseases and Vaccinology, National Health Research Institutes, No. 35 Keyan Rd, Zhunan, Miaoli 350, Taiwan; email: sckuo@nhri.edu.tw

Absence of SARS-CoV-2 Transmission from Children in Isolation to Guardians, South Korea

Eun Joo Lee, Dong Hyun Kim, Sung Hee Chang, Sun Bok Suh, Jina Lee, Hyunju Lee, Mi Seon Han

Author affiliations: Seongnam Citizens Medical Center, Seongnam, South Korea (E.J. Lee); Inha University Hospital, Incheon, South Korea (D.H. Kim); Seoul Medical Center, Seoul, South Korea (S.H. Chang); Busan Medical Center, Busan, South Korea (S.B. Suh); Asan Medical Center, University of Ulsan College of Medicine, Seoul (J. Lee); Seoul National University Bundang Hospital, Seoul National University College of Medicine, Seongnam (H. Lee); Seoul Metropolitan Government-Seoul National University Boramae Medical Center, Seoul (M.S. Han)

DOI: https://doi.org/10.3201/eid2701.203450

We explored transmission of severe acute respiratory syndrome coronavirus 2 among 12 children and their uninfected guardians in hospital isolation rooms in South Korea. We found that, even with close frequent contact, guardians who used appropriate personal protective equipment were not infected by children with diagnosed coronavirus disease.

Coronavirus disease (COVID-19) in children is known to occur mainly from family clusters (*1*). However, children can be the only infected members in a household, especially when COVID-19 is contracted from relatives or teachers. Such situations raise concerns about isolation because little information is available on transmission of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which causes COVID-19, during colocation of young children with their uninfected guardians. Although children generally are asymptomatic or have mild symptoms, they could be infective (*1*,*2*). We explored whether SARS-CoV-2 was transmitted from children to their uninfected guardians in a hospital isolation setting.

During February 18–June 7, 2020, we analyzed all children <19 years of age with COVID-19 and their uninfected guardians who were isolated together in 7 hospitals in South Korea. The infected children were encouraged to wear face masks. The guardians were advised to wear personal protective equipment (PPE), but the degree of PPE varied among hospitals. Adherence to PPE was monitored by the medical staff; compliance was judged as good when PPE was worn most of the time, fair for frequent adherence,

Article DOI: https://doi.org/10.3201/eid2701.203394

Nonpolio Enterovirus Activity during the COVID-19 Pandemic, Taiwan, 2020

Appendix

Methods

Data collection

National Health Insurance provides medical coverage for >99% of Taiwan citizens. It collects medical information of all beneficiaries including ICD-9-CM/ICD-10 codes. Aggregated data regarding outpatient and emergency room (ER) visits are retrieved from National Health Insurance and transferred to Taiwan CDC every week. These data are made public in the Taiwan National Infectious Disease Statistics System (https://nidss.cdc.gov.tw) (*1*). The ICD-9-CM/ICD-10 codes are used to identify hand-foot-and-mouth disease or herpangina (ICD-9-CM of 074.3 or 074.0, and ICD-10 of B08.4 or B08.5 respectively). The diagnoses of hand-foot-and-mouth disease or herpangina are mainly based on symptoms in Taiwan and the ICD-9-CM/ICD-10 codes of beneficiaries are transferred mandatorily to National Health Insurance.

Difference-in-differences model

A “difference-in-differences” model generates a causal estimate of the change in an outcome due to an intervention or exposure, after subtracting the expected background change observed in a reference group without the intervention or exposure. The strengths of this method include preservation of time order, accounting for changes in secular trends, and eliminating the pre-intervention differences in outcomes between the groups. Therefore, this model was used to

analyze data from outpatient department and ER visits for non-polio enterovirus (NPEV) infections. We assigned the whole population of outpatient department and ER visits during the 2019–2020 season to the "exposed" group. In this case, the "exposed" condition means that the population adhered to infection control measures after the first imported COVID-19 case (Figure 1). The populations of outpatient department and ER visits during the past 5 seasons were assigned to five "unexposed" groups. Since the National Health Insurance of Taiwan includes >99% of Taiwan residents, the risk of NPEV is calculated as the ratio of total weekly number of outpatient department and ER visits that yielded an NPEV diagnosis to the total weekly number of outpatient department and ER visits for all diseases.

The basic equation for the model is

$$\mu_{ij} = \beta_0 + \beta_{exp}\text{*Exposure} + \beta_{week} * \text{Week} + \beta_{interaction}\text{*Exposure*Week} + \varepsilon_{ij} \quad (1)$$

where μ_{ij} is the expected mean value for subject *i* at week *j*; Exposure is a binary indicator that the subject is exposed to the infection control measures; Week denotes the specific week; and ε_{ij} is the error term for the outcome measure of subject *i* at week *j*. Note that the outcome measure in this study is the total number of outpatient department and ER visits for NPEV, which is a counting variable. Therefore, in this case the μ_{ij} term on the left-hand side of the equation in Eq. (1) was replaced with $\log(\mu_{ij})$, and the equation is estimated via a Poisson regression model. Thus, the log link is specified and the coefficient estimates are on the log scale. Difference-in-difference values for the 2019–2020 season with respect to the 2014–2019 seasons are presented with a 95% CI. Negative values mean that fewer outpatient department and ER visits for NPEV were observed in the 2019–2020 season than in the 2014 to 2019 seasons.

Poisson regression model

The Poisson regression model was used to estimate the number of outpatient department and ER visits for NPEV per week and to analyze the weekly change in the number of visits for NPEV. The Poisson model is one of the generalized linear models (GLMs) that can deal with strictly positive response variables, such as counts and rates. We assumed that the weekly number of outpatient department and ER visits for NPEV follows a Poisson distribution. That is,

$$y_{ij} \sim \text{Poisson}(\mu_{ij}),$$

where y_{ij} represents the number of outpatient department and ER visits for NPEV in year *i* and week *j*, and μ_{ij} is the expected number of outpatient department and ER visits for NPEV. Our full model, which includes additional interaction terms with sub-periods of the season, is written below. W_{s_t} is a dummy variable for a range of weeks, defined as W_{s_t} = 1 if $s \le W \le t$; W_{s_t} = 0, otherwise. Y and W are dummy variables for the year and week; that is, they take the value 1 if the year or week is identical with the index i or j respectively.

$$\begin{aligned}\log(\mu_{ij}) = \log(N_{ij}) + \beta_0 + \beta_1 \mathrm{Y} + \beta_2 \mathrm{W} + \beta_3(\mathrm{W}_{1\_7})_{ij} + \beta_4(\mathrm{W}_{8\_11})_{ij} \\ + \beta_5(\mathrm{W}_{12\_15})_{ij} + \beta_6(\mathrm{W}_{16\_23})_{ij} + \beta_7(\mathrm{Y} * \mathrm{W})_{ij} + \beta_8(\mathrm{Y} * \mathrm{W}_{1\_7})_{ij} \\ + \beta_9(\mathrm{Y} * \mathrm{W}_{8\_11})_{ij} + \beta_{10}(\mathrm{Y} * \mathrm{W}_{12\_15})_{ij} + \beta_{11}(\mathrm{Y} * \mathrm{W}_{16\_23})_{ij} + \beta_{12}(\mathrm{W} * \mathrm{W}_{1\_7})_{ij} \\ + \beta_{13}(\mathrm{W} * \mathrm{W}_{8\_11})_{ij} + \beta_{14}(\mathrm{W} * \mathrm{W}_{12\_15})_{ij} + \beta_{15}(\mathrm{W} * \mathrm{W}_{16\_23})_{ij} \\ + \beta_{16}(\mathrm{Y} * \mathrm{W} * \mathrm{W}_{1\_7})_{ij} + \beta_{17}(\mathrm{Y} * \mathrm{W} * \mathrm{W}_{8\_11})_{ij} + \beta_{18}(\mathrm{Y} * \mathrm{W} * \mathrm{W}_{12\_15})_{ij} \\ + \beta_{19}(\mathrm{Y} * \mathrm{W} * \mathrm{W}_{16\_23})_{ij}\end{aligned}$$

This model has an equivalent representation as follows.

$$\log\left(\mu_{ij}/N_{ij}\right) = \beta_0+\beta_1 \mathrm{Y} + \beta_2 \mathrm{W} + \beta_3(\mathrm{W}_{1\_7})_{ij} + \beta_4(\mathrm{W}_{8\_11})_{ij}$$
$$+ \beta_5(\mathrm{W}_{12\_15})_{ij}+\beta_6(\mathrm{W}_{16\_23})_{ij} + \beta_7(\mathrm{Y}*\mathrm{W})_{ij} + \beta_8\left(\mathrm{Y}*\mathrm{W}_{1\_7}\right)_{ij}$$
$$+ \beta_9(\mathrm{Y}*\mathrm{W}_{8\_11})_{ij} + \beta_{10}(\mathrm{Y}*\mathrm{W}_{12\_15})_{ij} + \beta_{11}(\mathrm{Y}*\mathrm{W}_{16\_23})_{ij} + \beta_{12}(\mathrm{W}*\mathrm{W}_{1\_7})_{ij}$$
$$+ \beta_{13}(\mathrm{W}*\mathrm{W}_{8\_11})_{ij} + \beta_{14}(\mathrm{W}*\mathrm{W}_{12\_15})_{ij} + \beta_{15}(\mathrm{W}*\mathrm{W}_{16\_23})_{ij}$$
$$+ \beta_{16}(\mathrm{Y}*\mathrm{W}*\mathrm{W}_{1\_7})_{ij} + \beta_{17}(\mathrm{Y}*\mathrm{W}*\mathrm{W}_{8\_11})_{ij} + \beta_{18}(\mathrm{Y}*\mathrm{W}*\mathrm{W}_{12\_15})_{ij}$$
$$+ \beta_{19}(\mathrm{Y}*\mathrm{W}*\mathrm{W}_{16\_23})_{ij}$$

where N_{ij} is the weekly total number of outpatient department and ER visits for all diseases in year *i* and week *j*. $\log(N_{ij})$ acts as an offset in the model, which is used to account for the variation in the total number of outpatient department and ER visits for all diseases in different weeks and different years. The parameter β_0 is the intercept; β_1 to β_{19} are unknown parameters to be estimated. With the log link function, μ_{ij} is expressed as a linear function of the explanatory variables. All of the statistical analyses were performed using SAS software, Version 9.4 (SAS Institute Inc., Cary, NC, USA). All *p* values are two-sided and $p < 0.05$ was considered to be statistically significant.

Preventable Fraction among the unexposed

Preventable fraction among the unexposed (PF_u) is the proportion of incidents in the unexposed group that could have been prevented by exposure to infection control measures. It is calculated as

$$PF_u = 1 - RR \quad (2)$$

where *RR* is the relative risk. Risk for NPEV infections among the exposed is defined as the number of weekly outpatient department and ER visits for NPEV out of all individuals seeking health care in the 2019–2020 season. Risk for NPEV infections among the unexposed is

defined as the average number of weekly outpatient department and ER visits for NPEV out of the average number of individuals seeking health care in the 2014–2019 seasons. *RR* is the ratio of the risk in the exposed group to the risk in the unexposed group. The adjusted *RR* is a relative risk adjusted for the total number of outpatient department and ER visits for non-polio enteroviruses and for all diseases, respectively, at week 1. Poisson regression model was used to estimate the adjusted *RR* and the 95% confidence interval. Consequently, adjusted PF_u is obtained.

We also calculate the relative risk and preventable fraction among the unexposed in four age groups (0–2, 3–4, 5–9, and 10–14). These values are denoted by RR_i and $PF_{u,i}$ for an age group *i*. The PF_u defined in Eq. (2) for patients under age 15 is simply called overall PF_u.

Reference

1. Jian SW, Chen CM, Lee CY, Liu DP. Real-time surveillance of infectious diseases: Taiwan's experience. Health Secur. 2017;15:144–53. PubMed https://doi.org/10.1089/hs.2016.0107

Appendix Table 1. The number of visits for non-polio enteroviruses during the 2019–2020 versus 2014–2019 seasons for patients under age 15.

	Number of visits (Week 47-Week 23)	
Characteristic	2019–2020	2014–2019 (Average)
Overall	81,942	205,979
Age group, y		
0–2	26,439	61,255
3–4	24,039	62,541
5–9	26,257	68,403
10–14	5,207	13,780
Hospital setting		
Emergency room	3,784	10,018
Outpatient department	78,158	195,961

Appendix Table 2. Difference in the estimated number of outpatient department and emergency room (ER) visits for non-polio enteroviruses (NPEV) during the 2019–2020 season compared to the 2014–2019 seasons for patients under age 15

	Estimated No. of visits		Difference-in-difference value in 2019–2020 vs
Calendar week	2019–2020 season	2014–2019 seasons	2014–2019 seasons (95% CI)[a,b,c]
47	7384	10756	
48	6502	10308	
49	6015	9876	
50	6456	9650	
51	5613	8879	
52	4985	8481	
1	5844	8337	1006 (514, 1542)
2	5177	7004	1672 (1336, 2032)
3	4802	6517	1784 (1522, 2062)
4	4236	5941	1793 (1544, 2058)
5	2511	5112	898 (710, 1101)
6	2308	3352	2456 (2233, 2702)
7	1644	3174	1969 (1772, 2194)
8	1628	3081	2046 (1759, 2394)
9	1346	3202	1643 (1480, 1829)

Calendar week	Estimated No. of visits		Difference-in-difference value in 2019–2020 vs 2014–2019 seasons (95% CI)[a,b,c]
	2019–2020 season	2014–2019 seasons	
10	1337	3178	1658 (1487, 1856)
11	1269	3263	1506 (1265, 1803)
12	1324	3604	1219 (965, 1533)
13	1186	4045	640 (483, 822)
14	996	4077	419 (278, 582)
15	1077	4389	187 (−36, 468)
16	1092	5582	**−991 (−1172, −773)**
17	979	6648	**−2170 (−2305, −2013)**
18	949	7656	**−3208 (−3315, −3086)**
19	974	8752	**−4278 (−4374, −4173)**
20	1008	10213	**−5706 (−5803, −5599)**
21	957	11852	**−7396 (−7501, −7278)**
22	1089	13451	**−8863 (−9008, −8696)**
23	1226	15612	**−10886 (−11084, −10651)**

[a]Subtraction of differences before week 1 from week 1 to 23 differences. Negative values represented fewer NPEV outpatient department and ER visits in the 2019–2020 season vs the 2014–2019 seasons.

[b]Normalized by the total number of outpatient department and ER visits for NPEV at baseline (weeks 47–52) to eliminate the pre-intervention differences in outcomes between the groups (the 2019–2020 season versus the average of five previous seasons). The variation in the total number of outpatient department and ER visits for all diseases in different weeks and different years had been adjusted through the offset in the model.

[c]The decrease with statistical significance was indicated by bold type.

Appendix Table 3. Difference in the estimated number of outpatient department and emergency room (ER) visits for non-polio enteroviruses (NPEV) during 2019–2020 compared to the 2014–2019 seasons in different age groups

Calendar	Difference-in-difference value in 2019–2020 vs 2014–2019 seasons (95% CI)[a,b,c]			
week	Age 0–2	Age 3–4	Age 5–9	Age 10–14
1	925 (773, 1094)	331 (173, 503)	**−226 (−428, −4)**	−27 (−63, 13)
2	865 (772, 966)	499 (394, 612)	188 (44, 343)	49 (23, 76)
3	968 (894, 1048)	581 (499, 669)	198 (86, 317)	56 (36, 77)
4	945 (879, 1016)	590 (512, 673)	256 (147, 373)	58 (39, 78)
5	798 (739, 863)	291 (228, 358)	**−128 (−203, −46)**	17 (3, 32)
6	1130 (1054, 1215)	682 (612, 758)	466 (382, 560)	150 (132, 170)
7	935 (865, 1015)	522 (462, 590)	341 (269, 426)	120 (103, 138)
8	999 (902, 1118)	597 (511, 704)	327 (222, 461)	92 (69, 121)
9	937 (880, 1003)	508 (457, 568)	185 (123, 257)	51 (39, 65)
10	970 (909, 1040)	466 (414, 527)	174 (109, 251)	64 (51, 79)
11	945 (860, 1050)	373 (306, 459)	95 (4, 211)	70 (51, 94)
12	958 (862, 1077)	292 (220, 382)	−68 (−159, 51)	43 (24, 69)
13	742 (685, 807)	139 (94, 192)	**−251 (−309, −182)**	−4 (−16, 10)
14	644 (593, 705)	100 (57, 151)	**−286 (−338, −223)**	**−33 (−42, −21)**
15	512 (433, 612)	58 (−9, 143)	**−323 (−405, −215)**	**−61 (−76, −40)**
16	287 (220, 368)	**−352 (−402, −291)**	**−830 (−896, −747)**	**−98 (−112, −81)**
17	−13 (−64, 46)	**−696 (−734, −650)**	**−1270 (−1320, −1211)**	**−184 (−194, −172)**
18	**−306 (−347, −260)**	**−1007 (−1038, −972)**	**−1642 (−1682, −1596)**	**−259 (−267, −250)**
19	**−614 (−650, −574)**	**−1319 (−1345, −1290)**	**−2014 (−2049, −1974)**	**−342 (−350, −334)**
20	**−956 (−993, −916)**	**−1747 (−1774, −1718)**	**−2551 (−2587, −2511)**	**−455 (−463, −447)**
21	**−1374 (−1415, −1328)**	**−2224 (−2254, −2191)**	**−3159 (−3198, −3115)**	**−604 (−612, −595)**
22	**−1758 (−1812, −1696)**	**−2706 (−2746, −2659)**	**−3693 (−3747, −3628)**	**−718 (−729, −705)**
23	**−2252 (−2323, −2167)**	**−3297 (−3351, −3231)**	**−4451 (−4525, −4359)**	**−893 (−909, −874)**

[a]Subtraction of differences before week 1 from week 1 to 23 differences. Negative values represented fewer NPEV outpatient department and ER visits during the 2019–2020 season vs the 2014–2019 seasons.

[b]Normalized by the total number of outpatient department and ER visits for NPEV at baseline (weeks 47–52) to eliminate the pre-intervention differences in outcomes between the groups (the 2019–2020 season versus the average of five previous seasons). The variation in the total number of outpatient department and ER visits for all diseases in different weeks and different years had been adjusted through the offset in the model.

[c]The decrease with statistical significance was indicated by bold type.

Appendix Table 4. Difference in the estimated number of outpatient department or emergency room (ER) visits for non-polio enteroviruses (NPEV) during the 2019–2020 season compared to the 2014–2019 seasons for patients under age 15

	Difference-in-difference value in 2019–2020 vs 2014–2019 seasons (95% CI)[a,b,c]	
Calendar week	Outpatient department	Emergency room
1	896 (414, 1423)	78 (50, 110)
2	1553 (1224, 1905)	108 (88, 129)
3	1683 (1426, 1956)	92 (79, 107)
4	1669 (1427, 1927)	178 (159, 198)
5	825 (645, 1020)	164 (144, 186)
6	2419 (2201, 2660)	**−31 (−42, −18)**
7	1942 (1750, 2161)	0 (−11, 13)
8	1964 (1684, 2307)	73 (57, 93)
9	1559 (1400, 1740)	98 (86, 112)
10	1581 (1412, 1775)	77 (68, 88)
11	1435 (1198, 1730)	67 (55, 83)
12	1175 (925, 1486)	48 (35, 64)
13	631 (476, 811)	8 (0, 17)
14	432 (295, 593)	**−21 (−31, −9)**
15	210 (−10, 488)	**−18 (−28, −4)**
16	**−939 (−1116, −725)**	**−57 (−68, −44)**
17	**−2062 (−2195, −1908)**	**−112 (−119, −104)**
18	**−3046 (−3152, −2926)**	**−159 (−165, −152)**
19	**−4070 (−4163, −3966)**	**−208 (−214, −202)**
20	**−5434 (−5529, −5328)**	**−266 (−272, −259)**
21	**−7049 (−7152, −6933)**	**−336 (−341, −329)**
22	**−8419 (−8561, −8255)**	**−443 (−452, −432)**
23	**−10317 (−10513, −10083)**	**−555 (−567, −541)**

[a]Subtraction of differences before week 1 from week 1 to 23 differences. Negative values represented fewer NPEV outpatient department or ER visits in the 2019–2020 season vs the 2014–2019 seasons.

[b]Normalized by the total number of outpatient department or ER visits for NPEV at baseline (weeks 47–52) to eliminate the pre-intervention differences in outcomes between the groups (the 2019–2020 season versus the average of five previous seasons). The variation in the total number of outpatient department or ER visits for all diseases in different weeks and different years had been adjusted through the offset in the model.

[c]The decrease with statistical significance was indicated by bold type.

Appendix Table 5. Weekly Estimated Preventable Fraction among the unexposed (PF_u) from week 16-week 23 of year 2020, compared to the same weeks in the previous five seasons[a] in different age groups. The PF_u here was adjusted by total number of outpatient department and emergency room visits for non-polio enteroviruses and for all diseases, respectively, at week 1

	Estimated Preventable Fraction among the unexposed (95% CI)[a]				
Calendar week	Overall	Age 0–2	Age 3–4	Age 5–9	Age 10–14
16	0.17 (0.05, 0.28)	0.09 (−0.06, 0.22) [b]	0.14 (0.01, 0.25)	0.13 (−0.01, 0.25) [b]	0.04 (−0.10, 0.16) [b]
17	0.29 (0.20, 0.36)	0.21 (0.10, 0.30)	0.26 (0.16, 0.34)	0.26 (0.16, 0.34)	0.19 (0.09, 0.27)
18	0.38 (0.33, 0.44)	0.31 (0.24, 0.38)	0.36 (0.30, 0.42)	0.36 (0.30, 0.42)	0.31 (0.25, 0.37)
19	0.47 (0.43, 0.51)	0.40 (0.35 0.45)	0.45 (0.40, 0.49)	0.46 (0.41, 0.50)	0.41 (0.37, 0.46)
20	0.54 (0.51, 0.58)	0.48 (0.43, 0.52)	0.52 (0.48, 0.56)	0.53 (0.50, 0.57)	0.50 (0.47, 0.54)
21	0.61 (0.57, 0.64)	0.55 (0.50, 0.59)	0.59 (0.55, 0.62)	0.60 (0.56, 0.64)	0.58 (0.54, 0.61)
22	0.66 (0.62, 0.69)	0.61 (0.56, 0.65)	0.64 (0.60, 0.68)	0.66 (0.62, 0.70)	0.64 (0.61, 0.68)
23	0.71 (0.67, 0.74)	0.66 (0.61, 0.70)	0.69 (0.65, 0.73)	0.71 (0.67, 0.75)	0.70 (0.66, 0.73)

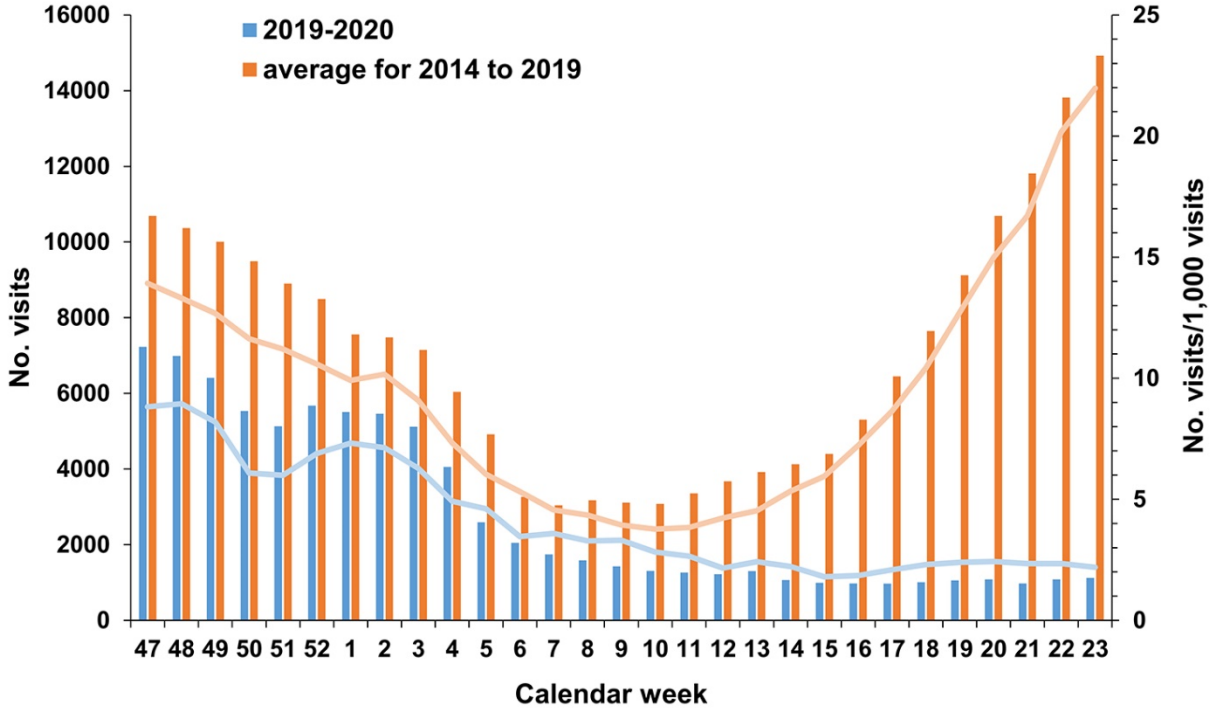
[a]Normalized by the total number of outpatient department and emergency room visits for non-polio enteroviruses and for all diseases, respectively, at week 1.

[b] All values were statistically significant except those underlined.

Appendix Table 6. Weekly Estimated Preventable Fraction among the unexposed (PF_u) from week 16-week 23 of year 2020, compared to the same weeks in the previous five seasons in different hospital settings

	Estimated Preventable Fraction among the unexposed (95% CI)[a]	
Calendar week	Outpatient department	Emergency room
16	0.73 (0.67, 0.78)	0.63 (0.53, 0.71)
17	0.76 (0.72, 0.80)	0.68 (0.61, 0.74)
18	0.79 (0.76, 0.82)	0.72 (0.67, 0.76)
19	0.82 (0.80, 0.84)	0.76 (0.72, 0.79)
20	0.84 (0.83, 0.86)	0.79 (0.76, 0.81)
21	0.86 (0.85, 0.88)	0.81 (0.79, 0.84)
22	0.88 (0.86, 0.90)	0.84 (0.81, 0.87)
23	0.90 (0.87, 0.91)	0.86 (0.82, 0.89)

[a]All values were statistically significant.



Appendix Figure. Non-polio enterovirus activity in Taiwan during 2019–2020 compared to the average of 2014–2019 for patients under age 15. The line represents the hand-foot-and-mouth disease or herpangina diagnoses per 1,000 visits. The bar represents the number of outpatient department and emergency room visits in which a diagnosis of hand-foot-and-mouth disease or herpangina was made.