Risk Factors for Hand, Foot, and Mouth Disease and Herpangina and the Preventive Effect of Hand-washing

WHAT'S KNOWN ON THIS SUBJECT: Hygiene and social distancing are recommended control measures for hand, foot, and mouth disease and herpangina. However, empirical data to support this recommendation are limited.

WHAT THIS STUDY ADDS: We found a strong protective effect from better hand-washing habits during an outbreak of hand, foot, and mouth disease and herpangina. A reduction in risk of >95% was supported by a consistently increasing dose-response effect after controlling for other exposures.

abstract

FREE

BACKGROUND: Hygiene and social distancing are recommended control measures for hand, foot, and mouth disease (HFMD) and herpangina. However, empirical data to support this recommendation are limited.

METHODS: During an outbreak of HFMD and herpangina due to infection by the human enterovirus 71, we defined a case as a vesicular papular rash on the hands, feet, buttocks, or oral mucosa and onset from April 30 to June 26, 2008. We selected 176 HFMD and herpangina case-children and a stratified random sample of 201 asymptomatic control-children; frequency matched according to residency status. We administered a questionnaire to the parents about their children's exposures and hygienic behaviors.

RESULTS: Risk factors for HFMD and herpangina included playing with neighborhood children (odds ratio [OR]: 11 [95% confidence interval (CI): 6.2–17]), visiting an outpatient clinic for another reason ≤ 1 week before onset (OR: 20 [95% CI: 5.0–88]), and community exposures to crowded places (OR: 7.3 [95% CI: 4.1–13]). By using a score summarizing responses to 4 hand-washing questions, we found that 50% of the case-children and 2.5% of control-children had a poor score of 1 to 3, whereas 12% of the case-children and 78% of control-children had a good score of ≥7 (OR: 0.00069 [95% CI: 0.0022–0.022]) after we adjusted for residency, age, and community exposures by using logistic regression.

CONCLUSIONS: Hand-washing by preschool-aged children and their caregivers had a significant protective effect against community-acquired HFMD and herpangina from the human enterovirus 71 infection. *Pediatrics* 2011;127:e898–e904

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KEY WORDS

hand, foot, and mouth disease, herpangina, hand-washing, risk factors

ABBREVIATIONS

HEV71—human enterovirus 71
HFMD—hand, foot, and mouth disease
OR—odds ratio
CI—confidence interval

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Although human enterovirus 71 (HEV71) most often causes benign hand, foot, and mouth disease (HFMD) and herpangina, it has caused clusters or outbreaks of severe neurologic and pulmonary disease with high mortality in young children.[1–13] Transmission of HEV71, as with other enteroviruses, is assumed to be person to person, from feces or oropharyngeal secretions to the mouth, nose, or eyes, transferred via hands or fomites.[14] Hence, hygienic measures and social distancing have been recommended as control and prevention measures for HEV71. However, empirical evidence to support this mode of transmission and these control measures is limited to a few studies,[15–17] showing weak or no association with kindergarten attendance or household crowding.

From April through June 2008, an HFMD and herpangina epidemic struck multiple mainland Chinese provinces. In response, on April 28, 2008, China made HFMD and herpangina a nationally notifiable disease and disseminated public health messages on hygiene and other preventive measures. From May 2 through June 18, 2008, the Yuhang District (population: 820 000) of Hangzhou Prefecture, Zhejiang Province, southeast China, reported 990 children with HFMD or herpangina, including 4 severe cases and 1 death. Of 306 patients with stool samples, 119 had polymerase chain reaction results that were positive for HEV71. A subset of 75 case-children also were tested for coxsackie A16; all results were negative. In early May, the Yuhang District government implemented control measures, including health education, disinfection, and closure of kindergartens with clusters of HFMD and herpangina. However, HFMD and herpangina continued to spread. From June 21 through June 26, we conducted an investigation in Qiaosi Township, where the incidence rate (321 per 100 000) was substantially higher than the rest of the Hangzhou Prefecture (50 per 100 000), to assess risk factors for transmission and to recommend control measures.

METHODS

Setting

Qiaosi Township has a population of 78 000, of which approximately half are economic migrants from other provinces or poorer areas of Zhejiang Province. A total of 90% of living quarters are supplied with a modern, piped, chlorinated water system. Private well water fills in the gaps in the public water supply, but water from these wells normally is used only for cleaning and washing. All houses have individual septic tanks. The township has 13 kindergartens, 1 primary hospital, and 13 community outpatient clinics.

Case Definition and Finding

We defined an HFMD or herpangina case as a vesicular papular rash on the hands, feet, buttocks, and/or oral mucosa in a resident of Qiaosi and illness onset from April 30 to June 26, 2008. During this period, all community clinics were instructed to refer all suspect HFMD and herpangina case-children to the Qiaosi or Yuhang hospitals for diagnosis and treatment. Community public health doctors cansvassed all houses to enumerate and obtain demographic data on all children and to find additional HFMD and herpangina case-children.

Case-Control Study

We enrolled all 273 children aged 6 years or younger with HFMD or herpangina in Qiaosi Township as case-children. From the enumeration of all children aged 6 years or younger, we selected a stratified random sample of 273 control-children who were frequency matched to the case-children by residency status (permanent resident or migrant).

Questionnaire and Interview

The questionnaire covered family information, exposures, and hand-washing habits. For the one-time or rare exposures, we asked about the exposure of case-children during the week before onset of the first symptom of HFMD or herpangina. For control-children, we asked about the entire 8-week outbreak period. We recruited and trained public health doctors from community health centers to conduct in-person interviews of parents (or other caregivers). If the interviewee was not at home, 1 revisit was attempted. We (Mr Ruan, Mr Yang, and Ms Jin) monitored the progress of each interviewer and checked all questionnaires for inconsistencies and missing data at the end of each day.

Bivariate Analysis

All analyses were stratified by residency (permanent and migrant) using the Mantel-Haentzel method. To adjust the difference in exposure duration for case-children (1 week) and control-children (8 weeks) for the 1-time or rare exposures, we divided the frequency reported by control respondents by 8 and then used logistic regression to calculate odds ratios (ORs) on the basis of a 1-week period.

Multivariate Analysis of Hand-Washing and Exposures

To assess the effectiveness of hand-washing, we assessed hand-washing frequency for each of 3 situations (after play, before eating, and by the caregiver before preparing food for the child). We selected these situations to focus on the expected modes of transmission (hand-to-hand-to-mouth and mouth-to-hand-to-mouth). For each situation, we used the following scores: 3, almost always; 1, sometimes; and 0, never. The words in Chinese that we used to describe frequency did not make a clear distinction between "always" and "often," so we combined those 2 levels (3, almost always). To cover other hand-washing situations, we used a question about the daily frequency of all hand-washing of the child. We summed the scores for each situation and the general frequency of hand-washing to compute an overall score for each individual. We then used logistic regression to assess the relationship between hand-washing and HFMD or herpangina risk. To control for potential confounding by other exposures, we repeated the above analysis using an overall exposure score. We scored each exposure variable as 0 (absent) or 1 (present) and used the sum of these variables as the overall score for other exposures. We then included this score in the logistic regression model along with the hand-washing score.

RESULTS

We identified 283 case-children with HFMD or herpangina in Qiaosi Township with illness onset between April 30 and June 26, 2008; 96% (273) of the children were aged 6 years or younger. Attack rates were highest (11%) in children aged between 1 and 2 years, and the lowest rates were found in infants (aged <1 year) and children aged 5 to 6 years (Table 1). The attack rate was 6.3% for boys and 5.9% for girls. Migrant children had a higher attack rate (9.9%) than permanent residents (2.9%). case-children lived throughout Qiaosi Township with no distinctive geographic pattern. After the initial health education, incidence did not rise appreciably until the last week of June (Fig 1).

Case-Control Study Findings

We successfully contacted the parents or other caregivers of 175 case-children and 201 control-children; all agreed to participate in the case-control investigation. Playing with neighborhood children, visiting an outpatient clinic for another illness during the week before HFMD or herpangina onset, and other infrequent community exposures that involved crowded places were important risk factors for HFMD and herpangina on the basis of the strength of association and proportion exposed (Table 2).

TABLE 1 Attack Rate of HFMD and Herpangina in Children Aged 6 Months to 6 Years: Qiaosi Township, Zhejiang Province, China, From April 30 to June 26, 2008

Age Group, y	No. of HFMD and Herpangina Cases	No. of Children	Attack Rate, %
0	18[a]	629	2.9
1	77	732	11
2	46	815	5.6
3	49	819	6.0
4	47	644	7.3
5	21	595	3.5
6	15	394	3.8
Total	273	4628	5.9

[a] All 18 children were between 6 and 11 months old.

Attending kindergarten or nursery school also was a risk factor; however, the association was much weaker (OR: 2.1 [95% confidence interval (CI): 1.3–3.4]) among the exposed age range (3–6 years). This lack of strong association was probably because of the fact that, during the outbreak, the township government closed 6 of 13 kindergartens with HFMD or herpangina clusters for 1 to 2 weeks and instituted special cleaning of 9 kindergartens that had single HFMD or herpangina case-children. The number of children or people in a home was not associated with increased risk, but the median number of children in a home was 1, which reflected the national "1-child" policy.

Health education about HFMD and herpangina, given in early May, had reached 82% of parents of case-children and 91% of control-children (OR: 0.45). The median age of both case-children and control-children was 3 years, but there was a statistically significant difference in the age distribution ($P < .05$; Kruskal-Wallis test). We did a stratified analysis of the data in Table 2 with additional stratification by age group (6 months to 1 year, 2–3 years, and 4–6 years), which showed only minor differences in the ORs and no changes in statistical significance of individual exposures (in addition to observing no heterogeneity of the OR among the age strata).

All 4 questions on hand-washing showed a protective effect from 80% to 98% (OR: 0.02–0.20) for the highest frequency of hand-washing

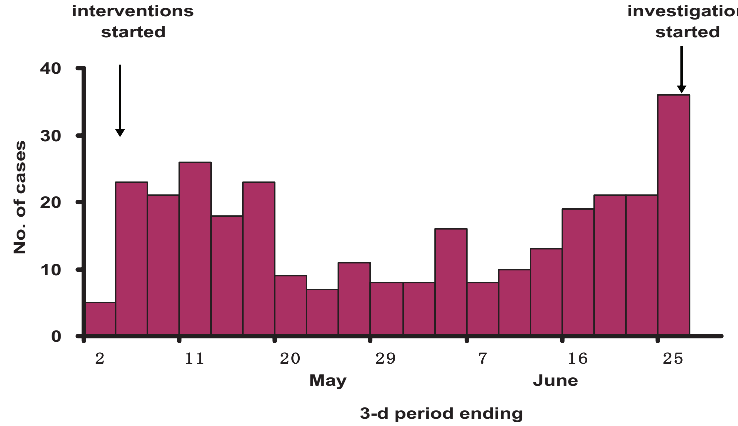

FIGURE 1
Date of onset for 273 children with HFMD, Qiaosi Township, Zhejiang Province, China, April 30 to June 25, 2008.

TABLE 2 Risk Factors for HFMD and Herpangina in 175 Case-Children and 201 Control-Children Aged 6 Months to 6 Years, Qiaosi Township, Zhejiang Province, China, From April 30 to June 26, 2008

Exposures	Exposure				OR[b]	95% CI
	Number[a]		Rate, %			
	Case	Control	Case	Control		
Family members, >3	119	117	68	58	1.4	0.88–2.3
Children in home, >1	28	32	16	16	1.1	0.59–2.0
Parents' education						
>9 y	12	16	6.9	8.0	0.62	0.21–1.8
1–9 y	134	161	77	80	0.73	0.38–1.4
0 y	27	24	16	12	Reference	—
Parent or caregiver did not know about HFMD or herpangina	31	18	18	9.0	2.20	1.20–4.10
Attended kindergarten or nursery school	70	48	40	24	2.10	1.30–3.40
Played with neighbor children	142	62	83	31	11	6.2–17
Sucks fingers	89	83	52	41	1.60	1.00–2.40
Went to a hospital[c]	31	22	18	11	20[d]	5.0–88[d]
Went to a party[c]	15	8	8.8	4.0	31[d]	2.2–433[d]
Went to a public place[c]	62	33	37	17	7.30[d]	4.10–13.00[d]
Frequently mentioned places[e]						
Fast food chain X	14	27	3.9	12	Reference[f]	—
Supermarket	207	89	57	41	5.10	2.40–11.00
Bus station	68	14	19	6.5	7.40	3.40–23.00
Amusement hall	33	10	9.1	4.6	6.10	2.20–19.00
Vaccination clinic	41	77	11	35	1.0	0.44–2.3
Hand-washing						
Uses soap	70	150	41	75	0.22	0.14–0.34
Frequency						
>7 per d	15	46	8.0	23	0.20	0.10–0.41
4–6 per d	56	89	33	44	0.38	0.23–0.63
1–3 per d	100	66	59	33	Reference	—
After play						
Almost always	19	125	11	62	0.04	0.02–0.08
Sometimes	55	50	32	25	0.29	0.16–0.52
Never	98	26	57	13	Reference	—
Before meal						
Almost always	26	151	15	76	0.02	0.01–0.05
Sometimes	48	35	28	18	0.19	0.09–0.39
Never	98	14	57	7.0	Reference	—
Adult washes hands before feeding child						
Almost always	39	136	23	68	0.04	0.02–0.08
Sometimes	59	56	34	28	0.13	0.06–0.29
Never	74	9	43	4.5	Reference	—

[a] Response rate for individual questions was from 97% to 100%.
[b] The OR was adjusted for residency status (permanent and migrant) by the Mantel Haentzel method.
[c] During the week before onset for case subjects and during the 8-week study period for control subjects.
[d] Adjusted by using logistic regression to equalize the exposure period of case and control subjects.
[e] Analysis of specific public places limited only to children who had visited a public place.
[f] Reference category for specific public places.

(Table 2). Compared with the poorest overall hand-washing level (score: 1–3) the protective effect of hand-washing became pronounced (>95% effective) with a score of ≥7 (Fig 2A). A score of 7 corresponds to having at least 1 "always" answer for any of the 3 situations (after play, before eating, and the caregiver washing hands before feeding the child). A total of 50% of case-children and 2.5% of control-children had a score of 1 to 3 compared with 12% of case-children and 78% of control-children with a score of ≥7, which gives the hand-washing score of ≥7 a protective effect of more than 99% (95% CI: 98% to >99%) after adjusting for residency and age (OR_{M-H}: 0.00069 [95% CI: 0.00022–0.022]).

To additionally adjust hand-washing for differences in exposure, we also created a score to represent the effect of multiple exposures. ORs increased from the reference level (1.0) to 35 as the number of different exposures increased (Fig 2B). Adjustment of hand-washing by this exposure score, age, and residency revealed little change in the protective effect of increased hand-washing (Fig 2C). Moreover, the hand-washing score of ≥7 retained a more than 99% (95% CI: 98% to >99%) protective effect (OR_{M-H}: 0.0043 [95% CI: 0.0011–0.017]).

DISCUSSION

The most striking finding in this HEV71 outbreak investigation was the exceptionally strong protective effect from better hand-washing habits among preschool-aged children and their parents. This effect, a more than 95% reduction in risk, was supported by a consistently increasing dose-response effect after controlling for other exposures. Community exposures other than kindergarten, preschool, or household exposures were the main contributors to HFMD and herpangina in this outbreak. Although the transmission continued after the local authorities instituted measures to control the outbreak in early May, we feel that their control measures actually had a strong mitigating effect on the course of the outbreak. The epidemic curve revealed a stable course throughout the 8-week period, and we observed relatively low attack rates in the high-risk age groups, despite intensive case finding. In comparison, intense transmission was occurring at the same time in many other sites in central China. Finally, the risk of HFMD and herpangina was lower among children whose parents had understood the health education messages. Qiaosi Township health authorities stressed hand-washing from the beginning of the outbreak, coincident with major

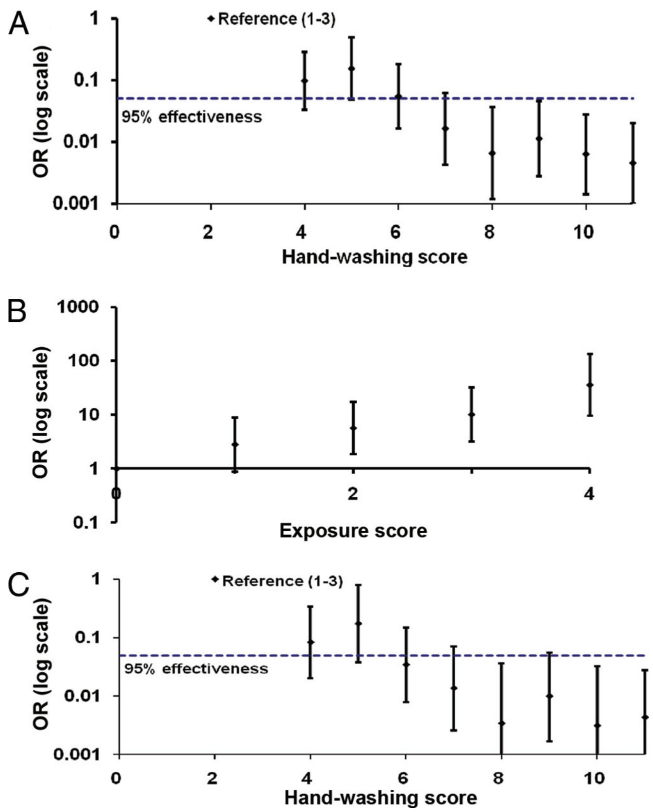

FIGURE 2
Change in OR for HFMD according to hand-washing score (A), exposure score (B) and hand-washing score adjusted by exposure score (C) for 175 case-children and 201 control-children from 6 months to 6 years old in Qiaosi Township, Zhejiang Province, China, April 30 to June 26, 2008. Error bars show point estimate and 95% confidence limits of the OR for each level of hand-washing and exposure scores. The reference level for hand-washing (1–3) is plotted as 2. The 95% effectiveness reference line is the prevented fraction in the exposed, equivalent to an OR of 0.05. The estimated change in the log odds for each unit increase in hand-washing score is -0.57 ($P < .01$) in A and for each unit of increasing exposure score is 3.4 ($P < .01$) in B.

national concern about severe or fatal infections. The high rate (>60%) of better hand-washing practices reflected in the control group attests to the effect of this advice.

A strong protective effect of hand-washing theoretically could be expected because HEV71 possesses many characteristics that would lead to transmission via contaminated hands. HEV71 is excreted directly from vesicles on the hands.[3,16,18–20] Viruses from the oropharynx and feces could contaminate hands as well. In addition, up to 40% of symptomatic HEV71 infections may have cough or coryza that could result in expelled, infectious droplets that could contaminate the hands directly or via fomites.[15,21] Finally, enteroviruses are relatively resistant to environmental conditions and would be expected to persist on hands and fomites for relatively long periods. Frequent hand-washing would have a proportionally greater effect of reducing transmission of enteroviruses than of less resistant organisms.[22,23] A relatively high specificity of HEV71 transmission to hands could contribute to the observed strong protective effect of hand-washing.

Studies that assessed the effect of hand-washing against other organisms, often done retrospectively during outbreaks, have involved hepatitis A, cholera, typhoid, norovirus, severe acute respiratory syndrome, echovirus, and *Campylobacter jejuni*.[24–33] These studies also report strong protective effects from self-reported hand-washing, ranging from 65% for severe acute respiratory syndrome to 93% for hepatitis A. Only 2 studies involved a respiratory agent (severe acute respiratory syndrome), and all estimated effects were smaller than what we report for HEV71. Unlike our investigation, these studies used a binary variable to analyze hand-washing, which could mask the effect of better levels of hand-washing.

Interventional studies of hand-washing to prevent respiratory diseases give far weaker effects. Meta-analyses of hand-washing intervention studies for acute respiratory infections estimate a protective effect of 16% to 24%.[34–37] Interventional studies have certain characteristics that tend to reduce the estimated effect. First, they lump together illnesses caused by many different infectious organisms in endemic settings where no single organism predominates.[34–36,38] The resulting risk ratios reflect an average of the effect of all individual organisms and could thus mask highly protective effects related to specific organisms. Interventional study designs compare reductions in average illness incidence to average group hand-washing. Lacking hand-washing comparisons to illness at the individual level, they cannot reveal the full potential of hand hygiene. Interventional studies in less-developed countries have greater effects,[36] probably because the initial average hand-washing level is relatively poor, allowing greater room for improvement. Finally, interventional studies need to modify hand-washing behavior, whereas observational studies do not. If the existing range of hand-washing efficiency is greater than the change in hand-washing behavior that an interventional study can achieve, the results on the basis of existing behaviors at the individual level should show a stronger effect.

The main limitation of our findings was that most exposures and preventive activities were determined retrospectively from parents or caregivers. For hand-washing and habitual exposures, such as play habits, differential overreporting or underreporting of hand-washing by parents of case- or control-children could bias our results to show a stronger or weaker effect than actually existed.

A second problem with recall involved asking about occasional or single exposures, such as visiting a hospital outpatient department. For case-children, the question covered the week before onset, but in dealing with an 8-week period, we could not expect valid answers about specific 1-week periods for control-children. To handle this recall problem, we asked about the entire 8-week period beginning with a memorable date (May 1, International Labor Day) for control-children and adjusted the responses to a 1-week period.

Many authors have proposed the development of vaccines for control of HEV71. We would propose that improved hand-washing and related hygienic improvement be instituted both in the community, nursery schools and kindergartens, and hospital outpatient and inpatient services. This may be particularly efficacious in areas of China and the world like Qiaosi Township, where quality water supplies and sanitation facilities already are installed.

In summary, during an outbreak of HFMD or herpangina from HEV71, hand-washing by preschool-aged children and their caregivers had an important mitigating effect and was highly protective at the individual level. In future HEV71 transmission seasons, we strongly recommend that local health authorities emphasize correct methods of hand-washing and the strong level of protection that parents can expect to see from their efforts.

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