Risk Factors of Enterovirus 71 Infection and Associated Hand, Foot, and Mouth Disease/Herpangina in Children During an Epidemic in Taiwan

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ABSTRACT. *Objective.* **In 1998, an enterovirus 71 (EV71) epidemic in Taiwan was associated with hand, foot, and mouth disease (HFMD)/herpangina and involved 78 fatal cases. We measured EV71 seroprevalence rates before and after the epidemic and investigated risk factors associated with EV71 infection and illness.**

Methods. **Neutralizing antibodies to EV71 were assayed for 539 people before the epidemic and 4619 people of similar ages after the epidemic. Questionnaires, which were completed during household interviews after the epidemic, solicited demographic variables, exposure history, and clinical manifestations.**

Results. **A total of 129 106 cases of HFMD were reported during the epidemic. Age-specific pre-epidemic EV71 seroprevalence rates were inversely related to age-specific periepidemic mortality rates ($r = -0.82$) or severe case rates ($r = -0.93$). Higher postepidemic EV71 seropositive rates among children who were younger than 3 years positively correlated with higher mortality rates in different areas ($r = 0.88$). After the epidemic, 51 (56%) of 91 younger siblings of elder siblings who were EV71-seropositive were EV71-seropositive; otherwise, 2.2% (4 of 186) of younger siblings were EV71-seropositive (matched odds ratio [OR]: 10; 95% confidence interval [CI]: 3.4–29). Stepwise multiple logistic regression revealed other factors associated with EV71 infection to be older age (adjusted OR: 2.5; 95% CI: 1.9–3.4), attendance at kindergartens/child care centers (adjusted OR: 1.8; 95% CI: 1.3–2.5), contact with HFMD/herpangina (adjusted OR: 1.6; 95% CI: 1.2–2.1), greater number of children in a family (adjusted OR: 1.4; 95% CI: 1.1–1.7), and rural residence (adjusted OR: 1.4; 95% CI: 1.2–1.6). Twenty-nine percent of preschool children who were infected with EV71 developed HFMD/herpangina. Younger age and contact with HFMD/herpangina were significant factors for the development of EV71-related HFMD/herpangina in these children.**

Conclusions. **An increased incidence of EV71 infection in young children occurred more often in geographic areas with increased mortality rates. Intrafamilial and kindergarten transmissions among preschool children were major modes of disease transmission during the widespread EV71 epidemic in Taiwan in 1998.** *Pediatrics* **2002;109(6). URL: http://www.pediatrics.org/cgi/content/full/109/6/e88; *enterovirus 71; hand, foot, and mouth disease; seroprevalence; transmission; risk factors; symptomatic ratio; reemerging infectious disease; Taiwan.***

ABBREVIATIONS. EV71, enterovirus 71; HFMD, hand, foot, and mouth disease; OR, odds ratio; CI, confidence interval; SD, standard deviation.

Enterovirus 71 (EV71) has been associated with outbreaks in the United States, Europe, Australia, Japan, Brazil, and Malaysia[1–10] since it was originally recognized in l969 in California.[1] Before 1998, 3 large outbreaks with dozens of fatal cases occurred in Bulgaria in 1975, Hungary in 1978, and Malaysia in 1997.[3,5,10] However, few studies have investigated the mode of transmission, the protective effect of preexisting EV71 antibodies, and the risk factors associated with EV71 infection as well as its clinical outcomes.

The largest and most severe EV71 epidemic to date occurred in Taiwan in 1998.[11–16] At that time, a total of 129 106 cases of hand, foot, and mouth disease (HFMD)/herpangina were reported; 405 cases had severe neurologic complications and/or pulmonary edema, and 78 children died.[15] A retrospective review found that sporadic cases of EV71 had occurred in Taiwan in 1980 and 1986.[15] In addition, sequences of some EV71 isolates in 1998 showed a high degree (92%) of identity in the VP-1 genomic region with that of the EV71 strain isolated in 1986.[17] Apparently, EV71 has circulated in Taiwan for at least 18 years; however, factors underlying the widespread increase of EV71 infection in 1998 remained unknown. Therefore, we initiated a community-based seroepidemiologic study to assess pre- and postepidemic immunity of Taiwanese populations to EV71. These measurements permitted description of the incidence of infection in the 1998 epidemic as well as the relationship between attack rates of severe or fatal cases and the EV71-seropositive rate, risk factors as-

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sociated with acquiring EV71 infection, and patterns of symptomatic EV71 infection.

METHODS

Surveillance and Definitions of Severe Enterovirus Cases During the Epidemic

During the 1998 epidemic, we used our nationwide sentinel physician surveillance and hospital surveillance systems to report uncomplicated and hospitalized HFMD/herpangina cases to Taiwan's Department of Health, according to a previously described method.[13,15] Although 129 106 cases of uncomplicated HFMD/herpangina were reported,[15] only severe cases were reviewed and verified by a committee established for that purpose.

Cases were defined as severe by the isolation of enterovirus or the presence of the symptoms/signs of HFMD/herpangina plus the occurrence of 1 or more complications such as aseptic meningitis, encephalitis, poliomyelitis-like syndrome, encephalomyelitis, pulmonary edema/hemorrhage, or death.[13,15] Herpangina included oral ulceration over anterior tonsillar pillars, the soft palate, buccal mucosa, or uvula. HFMD cases involved mouth ulcers plus a vesicular rash occurring on the hands, feet, knees, or buttocks. Aseptic meningitis was defined as a clinically compatible illness, with cerebrospinal fluid pleocytosis ($>5 \times 10^6$ leukocytes/L if the patient was older than 1 month, or $>25 \times 10^6$ leukocytes/L if the patient was a newborn) plus negative bacterial culture. Encephalitis showed an altered level of consciousness. Poliomyelitis-like syndrome was the occurrence of acute limb weakness plus decreased reflex and muscle strength. Encephalomyelitis included both encephalitis and poliomyelitis-like syndrome. Pulmonary edema/hemorrhage was defined as alveolar congestion on chest radiographs plus pink frothy fluid or blood from the endotracheal tube.

Study Design, Selection of Study Areas, and Data Collection for the Serosurvey

Cross-sectional studies before and after the 1998 EV71 epidemic were conducted. For pre-epidemic serum samples, we randomly selected 539 stored serum samples from healthy children who participated in vaccine trials or received health examinations in Chang Gung Children's Hospital between July and December 1997 and simultaneously from adults who received health examinations in Chang Gung Memorial Hospital. Chang Gung Memorial Hospital (3271 beds) and Chang Gung Children's Hospital (585 beds) are located in Taoyuan County and serve northern Taiwan.

Once the epidemic had ended, the institutional review board approved the study, serologic tests were performed, and questionnaire surveys were done by interview between January and July 1999 in both urban and rural areas. These areas included Taoyuan, Ilan, Taichung, and Kaohsiung counties in northern, eastern, western, and southern Taiwan, respectively, and the metropolitan areas of Taipei and Kaohsiung cities, located in northern and southern Taiwan, respectively. Urban areas were defined as areas with a population density of at least 1500 people per square kilometer, and rural areas were defined as those with 1499 or fewer people per square kilometer. In each study area, age- and gender-stratified sampling was conducted using household registration records. For obtaining better data on risk factors and family transmission, the sampled individuals and their family members were encouraged to donate blood samples and complete questionnaires after written informed consent was obtained.

The questionnaire solicited demographic data, residential area, number of children and adults in a family, history of HFMD/herpangina before or during 1998, intrafamilial or outside contact with HFMD/herpangina cases in 1998, family members with HFMD/herpangina before 1998, classmates or neighbors with HFMD/herpangina in 1998, travel history, sources of water supply, employment of a babysitter, enrollment in a kindergarten or child care center, breastfeeding during infancy, and vaccination history. Contact with HFMD/herpangina cases was defined as kissing, hugging, shaking hands with, sharing food with, or playing with children who had HFMD/herpangina. Generally, both interviews and interviewees were well-informed because the local health bureaus and the mass media had aggressively implemented a public education program on symptoms/signs of HFMD/herpangina during the epidemic period. All interviewers were trained, and contact history information was collected from several family members to minimize recall bias. EV71 infection was defined as EV71 seropositivity and symptomatic EV71 infection as EV71 seropositivity plus a history of HFMD/herpangina.

Laboratory Methods for the EV71 Neutralizing Antibody

The neutralizing antibody test of EV71 followed the standard protocol of a plaque reduction neutralization test.[18,19] Serum samples were heat treated for 30 minutes at 56°C, serially diluted, mixed with 100 50% tissue culture-infective doses of EV71 TW/2272/98 strain (GenBank accession number AF119795), and then incubated for 2 hours at 37°C in microtiter plates seeded with rhabdomyosarcoma cells. Each plate included a cell control, serum control, and virus back-titration. Cytopathic effect was monitored from 2 to 7 days after incubation, and the serotiter was determined when the cytopathic effect was observed in 1 50% tissue culture-infective dose of the virus back-titration. Cells were fixed with 5% glutaraldehyde and stained with 0.1% crystal violet. Seropositivity was defined as a reciprocal of the serotiter ≥ 8.

Statistical Analyses

We analyzed the data with the SAS statistical software (version 6.12; SAS Institute, Cary, NC). We used the Student t test for continuous data and χ^2 tests appropriate for categorical data. Mortality rates and severe case rates used the 1998 census population as the denominator. Geographic difference in mortality rates was analyzed by goodness-of-fit χ^2 test. A simple linear regression was used to examine the strength and pattern of association for continuous outcome variables. The relationship of EV71 seropositivity in sibling pairs was assessed by McNemar χ^2 test with Yates correction. Univariate analysis was done to screen statistically significant variables. Then, a stepwise multiple logistic regression analysis was performed to adjust confounders simultaneously and to calculate the multivariate-adjusted odds ratios (OR) for risk factors.[20] The α level of model selection was set to be 0.15 for in-and-out models. $P < .05$ indicated statistical significance.

RESULTS

Pre-epidemic EV71-Seroprevalence Rates and Severe Clinical Outcome in Northern Taiwan

Figure 1 demonstrates how lower pre-epidemic EV71-seroprevalence rates in northern Taiwan were associated with mortality rates and severe case rates during the EV71 epidemic. The 3 lowest EV71-seroprevalence rates from July to December 1997 were those of children 6 months to 3 years of age, a group with a majority (86% [24 of 28]) of fatal and severe (69% [102 of 147]) cases. Linear regression analysis of these associations found that age-specific pre-epidemic EV71-seroprevalence rates inversely correlated with age-specific enterovirus-related mortality rates with a correlation coefficient (r) of -0.82 ($P = .004$) and with severe case rates with an r of -0.93 ($P < .001$).

Geographic Distribution of Mortality Rates and Postepidemic EV71-Seropositivity Rates Among Young Children

The geographic distribution of mortality rates was analyzed for children younger than 3 years, the group with the highest mortality rate. Mortality rates per 100 000 children of 3.8 in Taipei City, 1.9 in Kaohsiung City, and 15.8, 7.6, 2.0, and 5.0 in Taoyuan, Taichung, Kaohsiung, and Ilan counties, respectively, were statistically different ($\chi^2 = 15$; $P = .01$, goodness-of-fit χ^2 test). Taoyuan County had the

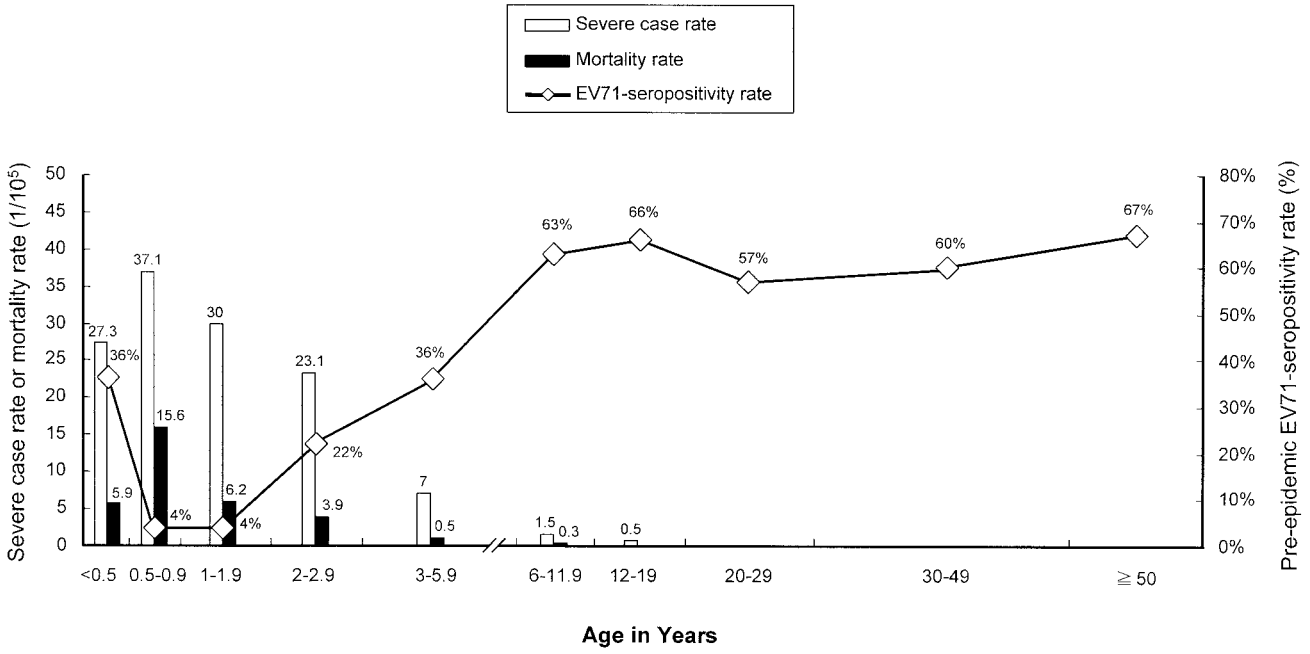

Fig 1. Age-specific EV71-seropositive rates before the EV71 epidemic and age-specific enterovirus-related mortality and severe case rates per 10^5 people in northern Taiwan during the EV71 epidemic. Age-specific pre-epidemic EV71 seroprevalence rates were inversely correlated with age-specific enterovirus-related mortality rates ($r = -0.82$; $P = .004$) and severe case rates ($r = -0.93$; $P < .001$). The numbers of pre-epidemic tested samples were 56, 48, 52, 23, 37, 48, 79, 70, 78, and 48 for age groups of <6 months, 0.5–0.9 year, 1–1.9 years, 2–2.9 years, 3–5.9 years, 6–11.9 years, 12–19 years, 20–29 years, 30–49 years, and >50 years, respectively.

highest mortality rate, and the 2 metropolitan areas, with the highest population densities, had 2 of lowest mortality rates for this high-risk age group.

The postepidemic EV71-seropositivity rates of the most susceptible children—those younger than 3 years—were 13% (12 of 93) in Taipei City, 33% (86 of 259) in Taoyuan County, 21% (30 of 144) in Taichung County, 10% (19 of 181) in Kaohsiung City, 22% (31 of 144) in Kaohsiung County, and 19% (31 of 166) in Ilan County ($\chi^2 = 39$; $P < .001$ with χ^2 test for differences among geographic regions). The EV71 seropositivity rate (25% [178 of 713]) in 4 counties was significantly higher than the rate (11% [31 of 274]) in the 2 metropolitan areas ($\chi^2 = 21$; $P < .001$ with χ^2 test). These seropositivity rates correlated with the same groups' mortality rates by region ($r = 0.88$; $P = .02$).

Detailed community-based, age-specific EV71-seropositivity rates in the 6 study areas after the epidemic are shown in Table 1. The higher mortality rates in children who were younger than 3 years were matched by age-specific change in seropositivity rates in all 6 study areas; children who were younger than 3 years had the largest increases in seropositivity from pre-epidemic (Fig 1) to postepidemic (Table 1).

Risk Factors Associated With EV71 Infection

In the analysis of risk factors for acquiring EV71 infection, we excluded infants who were younger than 6 months to prevent the effect of the maternal EV71 antibody and excluded people who were older than 6 years because their EV71 seropositive rates showed no significant increase from pre-epidemic (Fig 1) to postepidemic (Table 1). Of the 1800 remaining children, 554 were siblings from 277 families.

TABLE 1. Age-Specific EV71 Seropositivity Rates After the Epidemic in 4 Counties and 2 Major Cities of Taiwan

Age in Years	Taipei City*	Taoyuan County*	Taichung County*	Kaohsiung City*	Kaohsiung County*	Ilan County*	Total
<0.5	7% (29)	13% (56)	12% (43)	10% (48)	24% (55)	8% (60)	12% (291)
0.5–0.9	0% (30)	15% (54)	0% (42)	3% (58)	9% (54)	15% (60)	8% (298)
1–1.9	8% (39)	30% (102)	14% (58)	5% (82)	12% (65)	18% (61)	16% (407)
2–2.9	11% (35)	36% (97)	30% (60)	15% (81)	25% (32)	15% (60)	24% (365)
3–5.9	34% (70)	49% (224)	51% (97)	26% (137)	40% (141)	49% (61)	42% (730)
6–11	56% (69)	58% (168)	65% (86)	57% (166)	61% (211)	79% (61)	61% (761)
12–19	54% (48)	60% (160)	81% (114)	56% (166)	68% (99)	74% (61)	65% (648)
20–29	60% (42)	55% (93)	73% (60)	58% (55)	63% (48)	78% (60)	64% (358)
30–49	48% (84)	47% (91)	75% (77)	72% (88)	67% (89)	50% (60)	60% (489)
≥50	53% (38)	53% (36)	82% (55)	88% (25)	75% (57)	54% (61)	67% (272)
All ages	37% (484)	46% (1081)	54% (692)	40% (906)	49% (851)	44% (605)	46% (4619)

Numbers in parentheses are total numbers of tested samples.
* Blood samples were taken in Taoyuan, Kaohsiung, and Ilan Counties in January 1999, Taichung County in April 1999, Taipei City in May-June 1999, and Kaohsiung City in July 1999.

Fifty-six percent (51 of 91) of younger siblings were EV71 seropositive after the epidemic when their elder siblings were EV71 seropositive, whereas 2.2% (4 of 186) of younger siblings were EV71 seropositive when their elder siblings were EV71 seronegative ($\chi^2 = 28$; matched OR: 10; 95% confidence interval [CI]: 3.4–29; $P < .001$ with McNemar χ^2 test with Yates correction). The concordance rate of EV71 seropositivity among siblings was 84%.

In addition to sibling transmission, univariate analysis revealed that 8 factors—older age, attendance at a kindergarten/child care center, contact with HFMD/herpangina cases in 1998, a greater number of children in a family, residence in a rural area, classmates with HFMD/herpangina in 1998, family member(s) with HFMD before 1998, and tap-water usage—were significantly associated with EV71 infection (Table 2). After controlling for confounding factors in multivariate analysis, 5 factors—older age, attendance at a kindergarten/child care center, contact with HFMD/herpangina cases in 1998, a greater number of children in a family (Table 3), and residence in a rural area—remained significant risk factors associated with EV71 infection.

Age-Specific Rates and Risk Factors of EV71-Associated HFMD/Herpangina

Of the 484 preschool children who were EV71 seropositive after the epidemic, 29% (140 of 484) had HFMD/herpangina, although children who were 0.5 to 2.4 years of age had the highest rates of symptomatic EV71 infection (Table 4). Children who were younger than 6 months had the lowest rate of HFMD/herpangina. Otherwise, rates of HFMD/herpangina decreased as age increased.

Risk factors for HFMD/herpangina differed somewhat from those for EV71 infection measured by antibody acquisition. Among the 484 EV71-seropositive children, 74% (62 of 84) had developed HFMD/herpangina when family members had had HFMD/herpangina, 69% (20 of 29) had developed HFMD/herpangina when nonfamily contact of HFMD/herpangina had occurred, but only 16% (58 of 371) had HFMD/herpangina when contact with HFMD/herpangina had not occurred ($\chi^2 = 140$; $P < .001$, with χ^2 test).

TABLE 3. EV71 Seropositivity Rates After the Epidemic Among 1800 Children 6 to 72 Months of Age in Families With Different Numbers of Children

Number of Children	EV71 Seropositive Rate*	Adjusted OR†	95% CI
1	14% (355)‡	1.0	—
2	28% (857)	1.5	1.1–2.1
3	31% (394)	1.7	1.2–2.5
4	37% (118)	2.3	1.4–3.8
≥5	38% (76)	2.4	1.3–4.3

* Numbers in parentheses are total numbers of tested samples.
† Multivariate-adjusted OR calculated using the group with 1 child per family as the reference group and adjusted by age, kindergarten attendance, residential area, and contact with HFMD/herpangina.
‡ Mantel-Haenszel trend test, OR: 1.3; 95% CI: 1.2–1.4; $P < .001$.

DISCUSSION

Because polioviruses have nearly been eradicated, nonpolio enteroviruses remain an important cause of illness in the absence of vaccines and effective antiviral therapy.[6,9] One enterovirus, EV71, recently caused 2 large epidemics with many fatal cases in Malaysia and Taiwan[10,15] and was studied in Taiwan to delineate the seroepidemiologic background in which an EV71 epidemic occurred and the risk factors associated with EV71 infection and disease.

The inverse correlation between pre-epidemic seroprevalence and mortality or severe case rates reflects age-related disease susceptibility and the protective effect measured by specific antibody. Several independent risk factors for EV71 infection suggested that transmission occurred more frequently among families, in kindergarten/child care, and in rural areas.

The rate of HFMD/herpangina was lowest (14%) in EV71-seropositive infants who were younger than 6 months, and mortality and case-fatality rates in this age group were lower than those observed for children who were 0.5 to 1 year of age during the epidemic.[15] These data indicate that the preexisting

TABLE 2. Factors Associated with EV71 Infection in Preschool-Aged Children in Taiwan

Factors	Seropositive* ($N = 484$)	Seronegative* ($N = 1316$)	OR (95% CI)†	
			Unadjusted OR	Adjusted OR
Gender ratio (male/female)	1.03	1.10	1.1 (0.85–1.3)	
Age (mean ±SD)	3.9 ± 1.7	2.6 ± 1.7	3.8 (3.0–4.7)	2.5 (1.9–3.4)
Kindergarten/child care attendance	57%	29%	3.3 (2.7–4.1)	1.8 (1.3–2.5)
Contact history with HFMD/herpangina in 1998	23%	16%	1.6 (1.2–2.0)	1.6 (1.2–2.1)
Number of children in a family (mean ±SD)	2.5 ± 1.1	2.2 ± 1.1	1.6 (1.3–1.9)	1.4 (1.1–1.7)
Living in a rural area	55%	40%	1.4 (1.2–1.5)	1.4 (1.2–1.6)
Classmates with HFMD/herpangina in 1998	6%	4%	1.6 (1.0–2.6)	
Family member with HFMD/herpangina before 1998	13%	10%	1.4 (1.0–2.0)	
Water supply (using tap water)	74%	69%	1.3 (1.0–1.6)	
Neighbors with HFMD/herpangina in 1998	8%	6%	1.3 (0.88–2.0)	
Travel to high prevalence areas in 1998	27%	23%	1.2 (0.95–1.5)	
Ever breastfed	24%	24%	1.1 (0.93–1.3)	
Cared for by babysitters	6%	7%	1.1 (0.90–1.3)	

* EV71 seropositive or seronegative after the 1998 epidemic.
† OR was calculated using the seronegative children as a reference group. Unadjusted calculations were derived from univariate analyses. Adjusted OR resulted from multivariate analyses with a stepwise multiple logistic regression.

neutralizing antibody to EV71, acquired by transplacental transfer, was protective against severe outcomes of infection, similar to the protective effect of neutralizing antibodies against poliovirus or Coxsackie A21 virus.[21–23] Confirmation of this conclusion would require prospective follow-up of initially seronegative and seropositive cohorts through an epidemic.

We found that attending child care or kindergarten significantly increased the seropositive rates of anti-EV71, which is consistent with the double peaks of the 1998 Taiwan enterovirus epidemic curve. It demonstrated a larger peak in early June, a smaller peak in October, and a nadir during summer vacation (July to August).[15] Similarly, epidemics of EV71 spread from schools to the community at large.[24,25] Therefore, we recommend universal precautions as part of Taiwan's new public health policy, such as paying close attention to personal hygiene and handwashing, dissuading attendance by young children at child care centers or kindergartens, and isolating patients to limit the spread and reduce severe case rates when epidemics occur. However, the effect of these recommendations is hard to evaluate because, for ethical reasons, there is no control group after execution of the new public health policy.

From the seroepidemiologic data, it could be estimated that only 29% of preschool children who were EV71 seropositive after the epidemic had HFMD/herpangina. Of 177 culture-proven EV71 cases, 148 (84%) were found to have HFMD/herpangina by laboratory-based surveillance.[26] Thus, HFMD/herpangina was the major manifestation of EV71 illness, which suggests that up to 71% of the children with EV71 infection were asymptomatic and served as a reservoir for EV71 spread.

Contact with symptomatic EV71 cases was found to correlate positively with occurrence of EV71 infection and illness of HFMD/herpangina. This finding justifies a public health policy of excluding symptomatic patients from school/kindergarten to minimize multiple exposures to EV71 during class and play periods. Possible explanations for this phenomenon include a larger virus load, different modes of transmission, infection with a more virulent EV71 strain, or other social factors. These factors need additional study and are under investigation. We also found that the isolation rate of EV71 was significantly higher from throat swabs (93%) than from rectal swabs or feces (30%),[26] which suggests that additional routes of transmission other than the fecal-oral route might be possible during acute EV71 illness. In Coxsackie A21 virus, rates of infection and clinical illness were significantly higher by aerosol or nasal inoculation than by pharyngeal or oral inoculation.[23] Additional studies are mandatory to prove whether different routes of transmission will affect the transmissibility and severity of EV71.

TABLE 4. Age-Specific Percentage of Symptomatic (HFMD/Herpangina) Infection Among EV71-Seropositive Children

Age in Years During Blood Sampling (Age During the Epidemic)	Percentage of Children With Symptomatic Infection*
0.5–0.9 (<0.5)	14% (3/22)†
1–1.9 (0.5–1.4)	40% (25/63)
2–2.9 (1.5–2.4)	41% (36/87)
3–3.9 (2.5–3.4)	33% (20/61)
4–4.9 (3.5–4.4)	29% (22/76)
5–5.9 (4.5–5.4)	19% (34/175)
0.5–5.9 (<5.5)	29% (140/484)

* Number in parentheses is number of EV71-seropositive children with HFMD/HA divided by total number of EV71-seropositive children.
† $\chi^2 = 10.49$; $P = .001$ with Pearson χ^2 test.

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