Transmission and Clinical Features of Enterovirus 71 Infections in Household Contacts in Taiwan

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OUTBREAKS OF ENTEROVIRUS 71 have been documented since it was recognized in California in 1969.1 Fatalities in adults and children have been reported in Bulgaria, Hungary, and Malaysia.2-4 The largest and most severe enterovirus 71 epidemic occurred in Taiwan in 1998.5-10 The clinical syndromes and severity of cases were diverse. Thousands of cases of hand, foot, and mouth disease (HFMD) and herpangina occurred, 405 experienced severe neurological complications, such as encephalitis, meningitis, poliomyelitis, and/or pulmonary edema.9 Among the 405 complications, 78 children died.9

In a seroepidemiological study before and after the 1998 outbreak, we found that preepidemic and postepidemic enterovirus 71 seroprevalence rates in adults and children older than 6 years ranged from 57% to 67%.11 The postepidemic enterovirus 71 seropositive rates among children younger than 6 years ranged from 57% to 67%.11 The postepidemic enterovirus 71 seropositive rates among children younger than 6 years ranged from 57% to 67%.11 The postepidemic enterovirus 71 seropositive rates among children younger than 6 years ranged from 57% to 67%.11

Context Although enterovirus 71 has caused epidemics associated with significant morbidity and mortality, its transmission has not been thoroughly investigated.

Objectives To investigate enterovirus 71 transmission and determine clinical outcomes within households.

Design, Setting, and Participants Prospective family cohort study to investigate patients at a children's hospital in Taiwan and family members of these patients who had signs and symptoms suggestive of enterovirus 71 between February 2001 and August 2002. Patients and household members underwent clinical evaluations, virological studies, questionnaire-based interviews, and were followed up for 6 months.

Main Outcome Measures Enterovirus 71 infection, defined as a positive viral culture from a throat or rectal swab, or the presence of IgM or a 4-fold increase in neutralizing antibody in serum; and clinical syndromes, defined as asymptomatic; uncomplicated symptomatic; and complicated; with unfavorable outcomes of sequelae or death.

Results Ninety-four families (433 family members) had at least 1 family member with evidence of enterovirus 71 infection. The overall enterovirus 71 transmission rate to household contacts was 52% (176/339 household contacts). Transmission rates were 84% for siblings (70/83); 83%, cousins (19/23); 41%, parents (72/175); 28%, grandparents (10/36); and 26%, uncles and aunts (5/19). Of 183 infected children, 11 (6%) were asymptomatic and 133 (73%) had uncomplicated illnesses (hand, foot, and mouth disease, herpangina, nonspecific febrile illness, upper respiratory tract infection, encephalitis, or viral exanthema). Twenty-one percent (39/183) experienced complicated syndromes including the central nervous system or cardiopulmonary failure. During the 6-month follow-up, 10 died and 13 had long-term sequelae consisting of dysphagia in swallowing, cranial nerve palsies, central hypventilation, or limb weakness and atrophy. Age younger than 3 years was the most significant factor associated with an unfavorable outcome in children (P=.004). Among 87 infected adults, 46 (53%) were asymptomatic, 34 (39%) had nonspecific illnesses of fever, sore throat, or gastrointestinal discomfort, and 7 (8%) had hand, foot, and mouth disease. There were no complicated cases in adults.

Conclusions Enterovirus 71 household transmission rates were high for children in Taiwan and severe disease with serious complications, sequelae, and death occurred frequently. In contrast, adults had a much lower rate of acquisition of the infection and much less adverse sequelae.

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3 years old ranged from 0% to 36% \(^{11}\) and from 26% to 51% for 3- to 6-year-old children. Interestingly, only 29% of preschool children infected with enterovirus 71 developed HFMD and herpangina. Another Taiwanese seroepidemiological study \(^{12}\) examined serial serum antibody titers to enterovirus 71 in blood samples from 81 children born in 1988 (samples obtained yearly from 1989-1994 and from 1997-1999). Enterovirus 71 seroconversion occurred with a yearly incidence of 3% to 11% between 1989 and 1997. By 1997, 68% of the 81 children had serological evidence of enterovirus 71 infection. \(^{12}\) A seroepidemiological study in Singapore also demonstrated that the enterovirus 71 seroprevalence rate in the general population was as high as 60% to 70%. \(^{13}\) It is evident that enterovirus 71 infection is not uncommon and that documented cases do not accurately reflect the actual number of infections.

The reason why the 1998 enterovirus 71 outbreak in Taiwan was so large is not clear. \(^{9,10}\) Enterovirus 71 seropositivity was found to be concordant among siblings in our previous seroepidemiological study, suggesting that household transmission may play an important role in the spread of enterovirus 71. \(^{11}\) The secondary household transmission rates of enteroviruses, such as poliovirus, enterovirus 70, and coxsackievirus A24, vary. \(^{14,16}\) Transmission of enterovirus 71 among household family members needs further investigation. Such data are necessary to help control, manage, and prevent future enterovirus 71 infections. Therefore, the objectives of this study were to investigate enterovirus 71 transmission and determine clinical outcomes within households of patients infected with enterovirus 71.

**METHODS**

At Chang Gung Children’s Hospital in Taiwan, we studied patients who were suspected of having enterovirus 71 illnesses, such as HFMD and herpangina, and their household family members between February 2001 and August 2002. Institutional review board approval was obtained from the Chang Gung Memorial Hospital for this study and informed consent was obtained from all patients or their parents.

Patients presenting to the emergency department, outpatient clinic, or inpatient ward who had clinical syndromes suggestive of enterovirus 71 infection were asked to participate in the study along with their household family members. Throat and rectal swabs or stool samples for virus isolation and a blood sample for enterovirus 71 IgM neutralizing antibodies were obtained from the suspected cases of enterovirus 71 treated at Chang Gung Children’s Hospital. Clinical manifestations, disease course, and outcomes were recorded. Family members in the same household were asked to undergo screening with a throat swab and blood sample.

Questionnaire-based interviews were used to collect information about the family members, including demographic data, the number of bedrooms in the house, amount of contact time with the patient, presence and pattern of current or recent signs and symptoms (ulcers, sore throat, rash, fever, abdominal pain, and diarrhea), and contact history with persons outside of the household who had clinical syndromes suggestive of enterovirus 71 infection. Follow-up telephone interviews repeated questions about signs and symptoms at 2, 4, and 8 weeks. If any household family member reported experiencing signs or symptoms suggesting enterovirus 71 infection during the follow-up period, clinical assessment and laboratory investigation for enterovirus 71 were repeated. Patients with complications were followed up for 6 months at the hospital as outpatients or inpatients.

If the suspected case or any household family member tested positive for enterovirus 71, a second blood sample was obtained from the suspected case and household family members 4 weeks after the first blood sample. Household enterovirus 71 transmission rates and clinical outcomes were analyzed only for families with at least 1 member with evidence of enterovirus 71 infection.

**Clinical Syndromes, Outcomes, and Identified Source of Infection**

Laboratory evidence of enterovirus 71 infection was defined as the isolation of enterovirus 71 from a throat or rectal swab or stool sample, or the presence of enterovirus 71 IgM, or a 4-fold increase in enterovirus 71 neutralizing antibody serotiters between acute and convalescent sera samples.

In uncomplicated cases, evidence of HFMD included oral ulcers on the tongue and buccal mucosa and a vesicular rash on the hands, feet, knees, or buttocks. Evidence of herpangina included oral ulcerations on anterior tonsillar pillars, soft palate, buccal mucosa, or uvula. Nonspecific febrile illness was defined as a rectal temperature greater than 38°C without other symptoms. Enteritis was defined as diarrhea with or without abdominal pain. Upper respiratory tract infection was defined as sore throat, coryza, or cough without herpangina or rash.

In complicated cases, aseptic meningitis was defined as a clinically compatible illness with cerebrospinal fluid pleocytosis (≥5 leukocytes/mm\(^3\) in patients >1 month or ≥25 leukocytes/mm\(^3\) in neonates) and negative bacterial cultures. Encephalitis was characterized by an altered level of consciousness accompanied by cerebrospinal fluid pleocytosis. Evidence of a poliomyelitislike syndrome included acute limb weakness with diminished reflexes and muscular strength. A diagnosis of encephalomyelitis was made when there was evidence of encephalitis and poliomyelitislike syndrome. Cardiopulmonary failure was defined as pulmonary edema and hemorrhage with left ventricular failure requiring inotropic support. Unfavorable outcome was defined as death or sequelae and favorable outcome was defined as complete recovery after 6 months of follow-up.

The index cases were the first members of the household to have clinically apparent illness confirmed by laboratory studies. The secondary cases were defined as other family members whose enterovirus 71 symptoms occurred later than the index cases’ illness. Identified
source of enterovirus 71 infection within the household was defined as the first case in the household who displayed clinically apparent disease and who had had clear contact history with individuals outside the household who had illnesses suggestive of enterovirus 71 infection, such as HFMD and herpangina. The infection transmission interval was defined as the time between the onset of disease for the first case in the household and the onset of disease in a secondary case. A crowded household was defined as the ratio of the number of household members to the number of bedrooms greater than 1.5.

**Virus Isolation and Serotyping**

Throat swabs, rectal swabs, or stool samples were submitted for virus isolation. Samples were inoculated into human embryonic fibroblast, LLC-MK2, HEP-2, and rhabdomyosarcoma cell cultures. When enteroviral cytopathic effect involved more than 50% of the cell monolayer, cells were scraped and subjected to indirect fluorescent antibody staining with panenteroviral antibodies (Chemicon International Inc, Temecula, Calif). Isolates were identified as enterovirus 71 by immunofluorescence with enterovirus 71 monoclonal antibodies (Chemicon International).

**Enterovirus 71 Neutralizing Antibodies**

Laboratory methods for measuring enterovirus 71 neutralizing antibody followed standard protocol for the neutralization test on microtiter plates. Serum and 50 µL of enterovirus 71, containing 100 fifty percent tissue culture infective dose of enterovirus 71 strain TW/2272/98 (GenBank accession number AF119795), were mixed and incubated onto the microtiter plates with rhabdomyosarcoma cells at 35°C in a 5% carbon dioxide incubator. Each tested sample was run simultaneously with control, serum control, and virus back titration. Cytopathic effect was observed under an inverted microscope after an incubation period of 2 to 7 days, and the neutralizing antibody titer was determined at the time when cytopathic effect was observed in 1 fifty percent tissue culture infective dose of the virus back titration. The neutralizing antibody titer was defined as the highest dilution of serum that would prevent the occurrence of cytopathic effect. Seropositivity was defined as a neutralizing antibody titer of 8 or higher.

**Enterovirus 71 IgM Detection**

Enterovirus 71 isolate TW/2086/98 was amplified and purified as an antigen for m-capture enzyme-linked immunosorbent assay. Compared with the standard method of conventional virus culture, the sensitivity for m-capture enzyme-linked immunosorbent assay was 91.5% and the specificity was 93.1%.

### Statistical Analysis

Data were analyzed using SAS statistical software (Version 8.2, SAS Institute, Cary, NC). We used the t test for continuous variables and the χ² test for categorical data. Univariate analysis was used to screen for statistically significant variables; then forward stepwise multiple logistic regression analysis was
performed to adjust for confounders simultaneously and to calculate multivariable adjusted odds ratios (AORs) for risk factors of enterovirus 71 infection and an unfavorable outcome in children. The relative risk (RR) was calculated using the formula of Zhang and Yu,20 which corrects AORs obtained from logistic regression if the incidence of an outcome is higher than 10% in the study subjects. The α level of model selection was set at .15 for in and out models. P < .05 was considered statistically significant.

To adjust individual results within families, the PHREG program in SAS with STRATA option was used for conditional logistic regression analysis. Because the results were similar, only the stepwise multiple regression analysis results are reported.

RESULTS

One hundred seventy-three suspected cases of enterovirus 71 and their household members (343 children and 441 adults) were investigated between February 2001 and August 2002 (Figure). All eligible cases were included; 3 household members (2 fathers and 1 grandfather) refused to participate. Ninety-four families (54%) had at least 1 member with enterovirus 71 isolation and were studied further. The source of infection to the 94 families was only identified in 44 families (47%) (19% from relatives outside of the household, 13% from schoolmates, 11% from neighbors, and 4% from friends).

The enterovirus 71 infection transmission interval ranged from 1 to 15 days. The median transmission interval was 3 days and the mean (SD) interval was 3.7 (2.6) days. The enterovirus 71 transmission rate was 52% (176/339) among household contacts, including an 84% transmission rate for siblings (70/83); 83% for cousins (19/23); 41% for parents (7/275); 28% for grandparents (10/36); and 26% for uncles or aunts (5/19) (Table 1). The transmission rate was 84% (89/106) among household children and 37% (87/233) among household adults (P < .001). The 39% (41/106) culture-positive enterovirus 71 rate from household children was also significantly higher than the 4.3% (10/233) culture-positive enterovirus 71 rate from household adult contacts (P < .001).

Among children, no significant difference in the infection rate existed between siblings and cousins. Among adults, parents had a higher infection rate (41%; 72/175) than other adults (26%; 15/58) (P = .05). Infection rate for mothers (43%; 40/92) was similar to that for fathers (39%; 32/83) (P = .61). Enterovirus 71 seropositive rates for all family members were as high as 93% (401/429).

Enterovirus 71 infection rates declined as age increased (Table 2). Furthermore, all 71 children who were younger than 2 years were infected with enterovirus 71.

Factors Associated With Enterovirus 71 Infection in Children

Male sex and age younger than 6 years were associated with an increased risk of enterovirus 71 infection (Table 3). Children attending kindergarten or school had a lower incidence of enterovirus 71 infection. Having more household members, more children in the household, and a more crowded household did not significantly increase the risk of infection. Forward stepwise multiple logistic regression analysis indicated that the most significant factors associated with infection in children were age younger than 6 years (AOR, 9.11; 95% confidence interval [CI], 2.90-28.65; P < .001 and the corrected RR [CRR], 2.37; 95% CI, 1.74-2.68) and male sex (AOR, 4.11; 95% CI, 1.19-14.15; P = .03 and CRR, 1.13; 95% CI, 1.02-1.19).

Clinical Syndromes and Outcomes in Children

Children had significantly higher rates than adults of complications (21% vs 0%, P < .001) and long-term sequelae and fatalities (13% vs 0%, P < .001) (Table 4). The clinical outcome of the secondary cases was not significantly different from that of primary cases (P = .09).

Of 183 children, 10 (5%) died: 6 patients within 24 hours of hospitalization due to brainstem encephalitis plus fulminant cardiopulmonary failure; 3 patients within 2 to 7 weeks of hospitalization due to brainstem encephali-

<table>
<thead>
<tr>
<th>Table 2. Enterovirus 71 Infection Rates by Age Group*</th>
<th>Age Group, y</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≤6</td>
</tr>
<tr>
<td>Enterovirus 71 infection rate, No./total (%)</td>
<td>159/165 (96)</td>
</tr>
<tr>
<td>AOR (95% CI)[†]</td>
<td>1.00</td>
</tr>
<tr>
<td>CRR (95% CI)[‡]</td>
<td>1.00</td>
</tr>
</tbody>
</table>

*For all comparisons, P < .001.
†Calculated by using the group of those aged 6 years or younger as the reference and adjusted by sex.
‡Using the formula of Zhang and Yu to correct the AOR obtained from logistic regression.

| Table 3. Factors Associated With Enterovirus 71 Infection in Children* |
|----------------------------------------------------------|----------------|
|                                                          | Sex        | P Value  |
|                                                          | Male       | Female   | .003 |
| Age, mean (SD), y                                       | 3.3 (2.4)  | 10.0 (7.6) | .002 |
| Age ≤6 y                                                 | 158 (86)   | 6 (35)   | .001 |
| No. of household members ≥6                              | 95 (52)    | 9 (53)   | .94  |
| No. of children in household ≥3                          | 82 (45)    | 10 (59)  | .27  |
| Crowded household†                                       | 118 (64)   | 9 (53)   | .34  |
| Kindergarten or school attendance                       | 62 (34)    | 12 (71)  | .006 |

*Values expressed as number (percentage) unless otherwise indicated.
†Defined as the ratio of the number of household members to the number of bedrooms over 1.5.

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tis plus deep coma; and 1 patient with sequelae of dysphagia plus central hypoventilation at 4 months due to home ventilator dysfunction.

During the 6 months of follow-up, 13 (7%) children experienced long-term sequelae that involved the central nervous system. Magnetic resonance imaging findings revealed abnormal signal intensity in the brainstem and/or the spinal cord on T2-weighted images. Five patients had limb weakness and atrophy; 5 patients had swallowing dysfunction plus central hypoventilation plus limb weakness and atrophy; 1 patient had swallowing dysfunction plus central hypoventilation; 1 patient had limb weakness and atrophy plus abducens palsy; and 1 patient had abducens palsy alone.

Based on univariate analyses, age younger than 3 years was the most significant factor associated with long-term sequelae or death (Table 5). Contact history with a person outside the household with HFMD and herpangina, more household members, more children in the household, and living in a crowded household were not associated with a significantly higher unfavorable outcome rate. Children in kindergarten and school had lower unfavorable outcome rates. Forward stepwise multiple logistic regression analysis indicated that the most significant factor associated with an unfavorable outcome in infected children was age younger than 3 years (AOR, 6.19; 95% CI, 1.77-21.6; \( P = .004 \) and CRR, 5.18; 95% CI, 1.72-12.2), but there were no deaths in infants younger than 3 months.

### Table 4. Clinical Syndromes and Outcomes of Children and Adults With Enterovirus 71 Infection

<table>
<thead>
<tr>
<th>Clinical Syndromes and Outcomes</th>
<th>Children (n = 183)</th>
<th>Adults (n = 87)</th>
<th>( \text{P} ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymptomatic†</td>
<td>172 (94)</td>
<td>41 (47)</td>
<td>\n</td>
</tr>
<tr>
<td>Uncomplicated symptomatic</td>
<td></td>
<td></td>
<td>\n</td>
</tr>
<tr>
<td>Herpangina</td>
<td>19 (10)</td>
<td>8 (9)</td>
<td>.002</td>
</tr>
<tr>
<td>Nonspecific febrile illness</td>
<td>4 (2)</td>
<td>1 (1)</td>
<td>.68</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>16 (9)</td>
<td>18 (21)</td>
<td>.94</td>
</tr>
<tr>
<td>Enteritis</td>
<td>2 (1)</td>
<td>2 (2)</td>
<td>\n</td>
</tr>
<tr>
<td>Complicated symptomatic‡</td>
<td></td>
<td></td>
<td>\n</td>
</tr>
</tbody>
</table>
| HFMD plus encephalitis          | 11 (6)            | 0              | \n| HFMD plus polioike syndrome     | 5 (3)             | 0              | \n| HFMD plus encephalomyelitis and cardiopulmonary failure | 14 (8) | 0 | \n| Unfavorable outcomes§           | 23 (13)           | 0              | \n
Abbreviation: HFMD, hand, foot, and mouth disease.

*Values are expressed as number (percentage).
†For comparison between the rates of symptomatic cases of infected children and adults, \( P = .001 \) (measured with Pearson \( \chi^2 \) test).
‡For comparison between the rates of complicated symptomatic cases of infected children and adults, \( P < .001 \) (measured with Pearson \( \chi^2 \) test).
§For comparison between the rates of unfavorable outcomes between infected children and adults, \( P = .001 \) (measured with Pearson \( \chi^2 \) test). Of the 23, 13 had long-term sequelae and 10 died.

### Table 5. Factors Associated With Unfavorable Compared With Favorable Outcomes in Children With Enterovirus 71 Infection

<table>
<thead>
<tr>
<th>Factors Associated With Unfavorable Compared With Favorable Outcomes in Children With Enterovirus 71 Infection*</th>
<th>Unfavorable Outcomes (n = 23)</th>
<th>Favorable Outcomes (n = 160)</th>
<th>( \text{P} ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ≤3 y</td>
<td>20 (87)</td>
<td>83 (52)</td>
<td>.002</td>
</tr>
<tr>
<td>Males</td>
<td>15 (65)</td>
<td>97 (61)</td>
<td>.67</td>
</tr>
<tr>
<td>Secondary case in family</td>
<td>6 (26)</td>
<td>68 (46)†</td>
<td>.09</td>
</tr>
<tr>
<td>Contact history with HFMD and herpangina</td>
<td>12 (52)</td>
<td>110 (71)</td>
<td>.11</td>
</tr>
<tr>
<td>No. of household members ≥6</td>
<td>11 (48)</td>
<td>84 (53)</td>
<td>.68</td>
</tr>
<tr>
<td>No. of children in household ≥3</td>
<td>10 (43)</td>
<td>72 (45)</td>
<td>.89</td>
</tr>
<tr>
<td>Crowded household‡</td>
<td>15 (65)</td>
<td>103 (64)</td>
<td>.94</td>
</tr>
<tr>
<td>Kindergarten or school attendance</td>
<td>2 (9)</td>
<td>60 (38)</td>
<td>.01</td>
</tr>
</tbody>
</table>

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

*Unfavorable outcomes were defined as death or having long-term sequelae; and favorable outcomes as complete recovery.
†Because 11 of 160 infected children with favorable outcomes were asymptomatic, these 11 cases could not be defined as primary or secondary.
‡Defined as the ratio of the No. of household members to the No. of bedrooms over 1.5.

### Clinical Syndromes and Outcomes in Adults

Of 87 adults infected with enterovirus 71, 46 (53%) were asymptomatic (Table 4). All symptomatic adults recovered completely from uncomplicated illnesses, which included HFMD, herpangina, fever, upper respiratory tract infection, and viral exanthema.

### COMMENT

In this prospective family cohort study, we found that enterovirus 71 infections in young children are associated with serious disease; we also found a high household transmission rate for children. In contrast, infection in adults was less frequent and severe. Long periods of viral shedding may account for widespread transmission of enterovirus 71.14 In a previous study, we found enterovirus 71 to be present in infected patients for up to 5 weeks (based on stool sample analysis).21 Alternatively, previous research has demonstrated a higher rate of enterovirus 71 isolation from throat swabs (90%) than from rectal swabs or stool samples (32%).22 We speculate that respiratory transmission by large droplets from the oral cavity may also explain the high secondary infection rate within households in Taiwan, despite hand-washing precautions in practice since 1998.23 Therefore, isolation of infected patients within single rooms with masks for the patients and close contacts should be con-
cidered for the prevention of transmission of enterovirus 71.

New York Virus Watch data indicate that secondary coxsackievirus infections are more frequent in mothers (78%) than fathers (47%). However, in this study, enterovirus 71 infection rates were similar in the mothers (43%) and fathers (39%). Enterovirus 71 infection rates for parents (41%; 72/175) were higher than for other adults (26%; 15/58), suggesting that close or longer contact facilitated enterovirus 71 transmission.

Enterovirus 71 seropositive rates for all family members were as high as 93% (Table 1), which were significantly higher than those (57%-67%) for the general population in a previous seroepidemiological study. Therefore, it is likely that almost all the susceptible family members were infected once enterovirus 71 had been introduced in the household. Because the enterovirus 71 infection rate increased as age decreased, the most susceptible households with the youngest members had the highest enterovirus 71 infection rates. The high level of infection with enterovirus 71 is similar to that of poliovirus.

Among children, household transmission produced a higher rate of clinical symptoms (94%) compared with transmission outside the household (29%) in our previous enterovirus 71 seroepidemiological study. Viral load or host genetic factors may account for this difference. Because the rate of asymptomatic infection with enterovirus 71 after social contact is high (about 71%), it was difficult to identify the source of primary infections to the family. We were successful in determining the source in only 47% of cases.

Enterovirus 71 infections in adults were less serious than those in children. Although enterovirus 71 infection should be considered in cases of adult encephalitis, unexplained pulmonary edema, or cardiopulmonary failure, most infected adults in the present study were asymptomatic or experienced mild upper respiratory tract infections. The reasons why adults or older children have less severe illness needs further study. One possible reason for reduced severity might be that most adults and older children have antibody to enterovirus 71 or a related virus, whereas younger children may incur primary infections. Another possible reason is that inadequate hygiene of younger children may increase the viral load and produce more severe disease. Enterovirus 71 transmission by infected adults who are asymptomatic or mildly symptomatic is a likely source of many infections. In some families whose source of infection could not be identified, we speculate that enterovirus 71 infections might be introduced into the family by an asymptomatic adult. The transmission rates and outcomes of cases infected by contact with an asymptomatic case is unknown.

In conclusion, enterovirus 71 household transmission rates were high for children in Taiwan. In addition, enterovirus 71 was associated with serious complications, long-term sequelae, and death in children younger than 3 years. Adult enterovirus 71 infection was usually asymptomatic or mild.

Author Contributions: Dr Lin had full access to all of the data and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Chang, Hsu, Lin. Acquisition of data: Chang, Tsao, Hsia, Shih, C.-G. Huang, Hsu, Fang, Y.-C. Huang. Analysis and interpretation of data: Chang, Tsao, Hsia, Chan, Hsu, Y.-C. Huang, Lin. Drafting of the manuscript: Lin. Critical revision of the manuscript for important intellectual content: Tsao, Hsia, Shih, C.-G. Huang, Chan, Hsu, Fang, Y.-C. Huang, Lin. Statistical expertise: Chang, Hsu, Obtained funding: Chang, Lin. Administrative, technical, or material support: Tsao, Shih, C.-G. Huang, Lin. Study supervision: Lin.

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