

Important roles of public playgrounds in the transmission of hand, foot, and mouth disease

Y. H. XIE^{1,2,3}, V. CHONGSUUVIVATWONG^{2*}, Y. TAN¹, ZH-ZH. TANG¹,
V. SORNSRIVICHAI² AND E. B. McNEIL²

¹ *Acute Infectious Disease Control, Guangxi Zhuang Autonomous Region Centre for Disease Prevention and Control, Nanning, China*

² *Epidemiology Unit, Faculty of Medicine, Prince of Songkla University, Thailand*

³ *International Field Epidemiology Training Programme (IFETP), Bureau of Epidemiology, Ministry of Public Health, Thailand*

*Received 20 February 2014; Final revision 4 August 2014; Accepted 13 August 2014;
first published online 29 August 2014*

SUMMARY

Intra-home and kindergarten transmissions were the reported major modes of hand, foot, and mouth disease (HFMD) transmission in preschool children. However, infection at home is not common and 65–80% of cases do not attend preschool. We conducted a matched case-control study to explore the role of public playgrounds in the transmission of HFMD in addition to direct and indirect exposure to HFMD patients. We used 156 hospital source cases and 156 community source controls. Univariate analysis was followed by conditional logistic regression with attributable fraction computed. Adjusted odds ratios were 11·70 [95% confidence interval (CI) 1·26–109·40] for having HFMD cases in the same class, 14·19 (95% CI 3·55–56·74) for having HFMD cases within the 20 nearest neighbourhoods, 6·03 (95% CI 2·84–12·80) for exposure to public playgrounds, 2·13 (95% CI 1·05–4·32) for finger sucking and 0·29 (95% CI 0·11–0·78) for hand washing with soap before meals. The attributable fractions for the first four risk factors were 6·4%, 20·9%, 57·2% and 27·5%, respectively, while the population prevented fraction for hand washing with soap before meals was 18·7%. Based on our findings, hand washing with soap should be advocated. Health education could include topics which underline the precautions which need to be taken and the advice given regarding avoiding the use of public playgrounds during epidemic periods, especially when children have been getting sick.

Key words: Enterovirus, epidemics, epidemiology, infectious disease control, infectious disease epidemiology.

INTRODUCTION

Hand, foot and mouth disease (HFMD) is a common infectious disease in children aged <5 years. The main clinical manifestations are fever, sore throat, mouth

ulcers, rash or small vesicles on the hands, feet and mouth. HFMD is caused by a group of non-polio enteroviruses, particularly those belonging to the human enterovirus species A. The most common pathogens are coxsackievirus A16 (CV-A16) and enterovirus 71 (EV-A71).

Transmission of HFMD is from person to person by direct contact with respiratory droplets, faeces, blister fluid or through contact with a contaminated

* Author for correspondence: Dr V. Chongsuvivatwong, Epidemiology Unit, Faculty of Medicine, Prince of Songkla University, Hatyai, Songkhla, 90110, Thailand.
(Email: cvirasak@medicine.psu.ac.th)

environment [1–3]. Intra-home [4, 5] and kindergarten [4, 6–8] transmissions in preschool children have been well documented, leading to the policy of preschool closure and disinfection of toys, utensils and table surfaces for outbreak control [9–11]. However, around 65–80% of HFMD cases are non-preschool attendees [12, 13]. Implementation of screening for fever and rash before children enter preschool grounds was launched in China during 2008–2012, yet the epidemics were still not well controlled. There is a need to study the transmission outside preschools.

Exposure to a public place [14], visiting a hospital, eating out and shopping [15] were reported risk factors for HFMD. Adult hand washing, is also associated with risk reduction of HFMD in children [14, 16]. However, the magnitude of the contribution of adults exposed to HFMD in a community or at work who infect their children with the disease (indirect contact) is unknown. Most previous studies failed to report the attributable fraction, making it difficult to emphasize important measures for control in the population.

Guangxi is located in southern China and is one of the provinces with the largest epidemic of HFMD, having an incidence rate of 449·1/100 000 population and 117 fatalities in 2012. The epidemic season of HFMD in Guangxi is from April to July [17]. This study was conducted during the 2013 epidemic, with the aim of exploring the role of public playgrounds visited by children on the transmission of HFMD in addition to direct and indirect exposure to HFMD patients and personal hygiene.

METHODS

Study area

The study was conducted in Binyang County, Guangxi, which had a population of 785 977 in 2012. There are 2114 communities/natural villages in Binyang County, which include both urban areas and rural communities. From the surveillance data, the annual incidence rate of HFMD from 2008 to 2012 was 419/100 000 population. There are three county-level hospitals in Binyang, two (the People's Hospital of Binyang County and the Ninth People's Hospital of Nanning City) are designated hospitals for HFMD where all suspected cases are referred.

Study design

A matched case-control study with 1:1 ratio was chosen. Cases were identified from two designated

hospitals and controls were recruited from healthy children in the same community/natural villages as the cases. Comparison of contact history and exposure to HFMD was investigated in family members, preschools and 20 nearest neighbouring houses of the cases and controls.

Case recruitment

Cases were recruited from the HFMD clinics. During the study period, two researchers waited at the clinic, where patients with HFMD diagnosed by clinicians were immediately approached for consent to join the study. Those agreeing to join were examined by the researchers for fever, rash with blisters on the palms, soles, buttocks or mouth ulcers, using a checklist. Only patients having at least two typical symptoms were included in the study. Other criteria for eligibility included: (1) being a resident of Binyang County for at least 6 months; (2) aged ≤ 5 years. Those without a positive laboratory confirmation were excluded later. If there was more than one case in a household within the same outbreak, only the case first encountered in the hospital was included so that all cases in the study were relatively independent from each other.

Control selection

In order to ensure that the control came from the population at risk who did not develop the disease, the computerized database of vaccine immunization system from Binyang CDC was used. The system contains demographic information of all children. Based on the database, to ensure a balance in gender and age between cases and controls, we randomly selected a control with the same age (± 6 months) and gender, but not living in the same neighbourhood to avoid having the same exposure. After telephone explanation and appointment, exposure status of the control was assessed within 24 h after the case was recruited. Exclusion criteria for the control included: (1) having a rash on any part of the body at the time of interview; (2) prior participation in an EV-A71 vaccine clinical trial; (3) prior diagnoses of HFMD or herpangina; (4) having immunodeficiency or congenital heart disease; (5) diagnosed with measles, rubella or chicken-pox at the time of interview.

Sample size

Based on the formula of sample size calculation for a matched case-control study [18], and assuming that

27% of cases had contact history with a HFMD patient, in order to detect a threefold increase in the odds of the children who have a contact history with HFMD [4], 91 cases and 91 controls were required. Assuming that 35% of cases had exposure to public places, in order to detect a twofold increase in the odds of the children who were exposed to public places [14] the sample size for both cases and controls was 117. As all clinical diagnosis cases had to be laboratory confirmed and the expected positive rate was 70%, the total sample size was increased to 334.

Operational definitions

Direct contact was defined as the study subject (case or control) having body contact (e.g. hugging or shaking hands) or close contact (sharing toys, playing in the same playground, or staying in the same room including a classroom for more than 1 h) with a preceding HFMD case. If the subject's family member/caregiver at home or at preschool ever had body contact or close contact with a preceding case, the subject would be defined as having *indirect contact*. Being classified as having direct and indirect contact was not mutually exclusive.

Contact period of interest (both direct and indirect) was the 2–7 days before onset of disease for cases, and 2–7 days before interview for controls.

Neighbourhood was confined to the 20 nearest neighbouring houses or a radius of 200 m from the study subject's home (if the number of neighbouring houses was <20).

Public playground was defined as a public area where parents bring their children to play, including parks, children's play areas in department stores, rural grocery stores, public squares or other meeting places.

Data collection

Recruitment of consecutive cases and controls began on 21 March until the required sample size was achieved on 10 July 2013. Data were collected by face-to-face structured interviews of the study subjects' parents/guardian, their family members, caregivers at their preschools and 20 nearest neighbouring houses. The case and control were investigated in the same fashion. Variables included demographic information, contact history, personal habits of the study subjects and detailed contact history with HFMD cases of

their family members. We used three scales, i.e. 'seldom', 'often' and 'always' to measure personal habits, which is the classification used consistently by researchers. Within the 20 nearest neighbouring houses, we collected the number of children aged ≤ 5 years and the number of children diagnosed with HFMD 2–7 days before onset/interview from each household. We also collected general information, HFMD situation and contact history of each staff member in the preschools that the subjects attended.

The questionnaires and the throat and rectal swabs of cases were collected at the HFMD clinics after informed consent was obtained. An appointment for a home visit (within 2 days) was also made at the same time. Each control was followed up 7 days after being recruited to avoid misclassification. If the control was diagnosed with HFMD during this follow-up period, both the case and control would be excluded from the analysis.

Laboratory test method

The throat and rectal swabs were tested for enteroviruses using reverse transcriptase–polymerase chain reaction (RT–PCR). The reporting of pathogen results divided enteroviruses into three groups: EV-A71, CV-A16 and others. The procedure for laboratory testing followed the recommended protocol [19].

Data analysis

Data was analysed with R v. 3.0.1 (R Foundation, Austria) using the EPICALC and SURVEY packages. For univariate analysis, conditional odds ratios (ORs) and 95% confidence intervals (CIs) were provided with *P* value test using McNemar's χ^2 test. Proportion trend tests were used to explore the differences in personal habits and the exposure in public playgrounds. If the status of all the study subjects' neighbouring or preschool children were simply cross-tabulated against the status of the study subjects, there would be multiple records for each subject and the level of precision for association would be over-emphasized. Using survey analysis [20] with identification number of the study subject being the primary unit of analysis, Rao & Scott ORs (adjusting for multiple tests on the same subject) were obtained instead of simple ORs where the neighbour's effect on clustering over the same subject would be ignored. In multivariate conditional logistic regression, which adjusts for possible confounding factors, in order to reduce the complexity of analysis the

exposure status of the subject to his/her neighbour's status was dichotomized. The potential risk factors from univariate analysis with $P < 0.1$ were selected for inclusion in the multivariate conditional logistic regression models. The significance level for regression was set at < 0.05 . The ORs in the study were based on concurrent sampling process. Thus, it can be used to estimate the rate ratio.

The attributable fraction was used to measure the impact of the main exposure. Assuming HFMD is a rare disease and the controls represented the ≤ 5 years old population, the formula [21] for estimating the population attributable fraction for multiple risk factors is:

$$AR_C = 1 - \sum_j \frac{\rho_j}{R_j}$$

where AR_C is the attributable fraction, ρ_j is the proportion of all cases that are in stratum j , while R_j is the adjusted OR in stratum j . The total AR_T can be calculated from the formula $AR_T = 1 - \pi(1 - AR_C)$.

Ethical considerations

This study was approved by the Ethics Committee of the Faculty of Medicine, Prince of Songkla University and the Ethical Committee of Guangxi, China. Informed consent was obtained from the parents/guardians of all study subjects' and all the other study participants.

RESULTS

HFMD situation in Guangxi from 1 January to 10 July 2013

There were 93 614 HFMD cases with seven fatalities notified in Guangxi from 1 January to 10 July 2013. The incidence rate was 201.5/100 000 population. The male:female incidence ratio was 1.41:1. Over 95% of cases were aged ≤ 5 years of which preschool children accounted for 17.4%. A total of 967 cases were laboratory confirmed, the pathogens were identified as CV-A16 (25.8%, 250/967), EV-A71 (13.6%, 131/967) and other enteroviruses (60.6%, 586/967).

Case-control study findings

A total of 158 cases and 158 controls were recruited from 21 March to 10 July. Because one case tested negative for enteroviruses and one control developed HFMD during follow-up, two sets of children were

excluded from analysis. Thus 156 cases and 156 controls were included in the analysis.

CV-A16, EV-A71 and other enteroviruses were exclusively found in 57 (36.5%), two (1.3%) and 97 (62.2%) cases, respectively. The main manifestations were fever (123, 78.6%), rash with blisters on palms (152, 97.4%), soles (152, 97.4%), buttocks (95, 60.9%) and herpangina (135, 86.5%). Fever was more common in the other enterovirus infection compared to CV-A16 (OR 3.23, 95% CI 1.34–7.86), but there was no significant difference in other manifestations.

Of the cases, 630 family members, 3089 neighbouring houses and 175 staff from 29 preschools were investigated. The corresponding numbers for the controls were 620, 3102, 78 and 19, respectively.

Univariate analysis results

Univariate analysis results are summarized in Table 1. Compared to controls, cases were more likely to attend preschool, suck fingers and toys, less likely to wash their hands with soap, and preferred to visit public playgrounds and other places. Cases were also more likely to live with another HFMD case in the same house, share the same classroom at school, live near another HFMD case and live with a family member who had ever contacted a HFMD case within 2–7 days of onset. Of the significant risk factors, the proportion of cases exposed to public playgrounds was the highest. Around 69% of cases visited a public playground at least once a week and as many as 45% had ≥ 8 visits per week. The average time spent by those who visited a public playground was 59.1 min (S.D. = 39.4) per visit. Regular hand washing with soap both before meals and after playing had a protective effect.

A large majority of both cases and controls had no contact history at all. We therefore performed a subset analysis on those subjects without a contact history. Minor differences in results were observed and there were no changes in statistical significance of the exposure variables.

Multivariate conditional logistic regression results

Independent variables with a P value of < 0.1 from the univariate analysis and our main hypothesis variables were included in the initial multivariate conditional logistic regression model with each variable being dichotomized to initially screen for confounders. The

Table 1. *Univariate analysis of HFMD risk factors in Binyang County, Guangxi, China*

| Variable | Cases (<i>n</i> = 156) | Controls (<i>n</i> = 156) | OR (95% CI) | <i>P</i> value |
|--|-------------------------|----------------------------|-------------------|----------------|
| General information | | | | |
| Mean age (s.d.) | 2.0 (0.90) | 2.0 (0.85) | — | — |
| Gender (male) | 112 (71.8) | 112 (71.8) | — | — |
| Preschool attendance | 31 (19.9) | 19 (12.2) | 4 (1.34–11.97) | 0.013 |
| Main caregiver | | | | 0.903 |
| Parents | 95 (60.9) | 94 (60.7) | 0.971 (0.60–1.57) | |
| Grandparents | 61 (39.1) | 62 (39.3) | 1 | |
| No. of children aged ≤5 years in family | | | | 0.502 |
| 0 | 93 (59.6) | 83 (53.2) | 1 | |
| 1 | 57 (36.5) | 65 (41.7) | 0.79 (0.51–1.24) | |
| ≥2 | 6 (3.9) | 8 (5.1) | 0.68 (0.23–1.99) | |
| Mean (s.d.) | 0.52 (0.6) | 0.44 (0.57) | — | — |
| No. of children aged ≤5 years in 20 nearest neighbourhoods | | | | 0.917 |
| <5 | 13 (8.3) | 12 (7.7) | 1 | |
| 5–10 | 105 (67.3) | 103 (66) | 1.15 (0.44–2.99) | |
| >10 | 38 (24.4) | 41 (26.3) | 1.06 (0.38–2.99) | |
| Mean (s.d.) | 8.38 (3.0) | 8.8 (3.5) | — | — |
| Location of kindergarten* | | | | 0.641 |
| County/town | 20 (69) | 12 (63.2) | 1 | |
| Village | 9 (31) | 7 (36.8) | 0.19 (0.02–2.02) | |
| Type of kindergarten* | | | | 0.727 |
| Private | 26 (89.7) | 17 (89.5) | 1 | |
| Public | 3 (10.3) | 2 (10.5) | 1.50 (0.25–8.99) | |
| Kindergarten density (children/m ²)* | | | | 0.542 |
| 1–8 | 21 (72.4) | 15 (78.9) | 1 | |
| >8 | 8 (27.6) | 4 (21.1) | 2.11 (0.40–11.09) | |
| Class size (children)* | | | | 0.146 |
| 1–30 | 12 (41.4) | 12 (63.2) | 1 | |
| >30 | 17 (58.6) | 7 (36.8) | 2.17 (0.73–6.40) | |
| Personal hygiene | | | | |
| Sucks fingers | | | | <0.001† |
| Seldom | 75 (48.1) | 114 (73.1) | 1 | |
| Often | 37 (23.7) | 26 (16.7) | 2.56 (1.24–5.28) | |
| Always | 44 (28.2) | 16 (10.3) | 3.97 (2.03–7.76) | |
| Sucks toys | | | | 0.001† |
| Seldom | 73 (46.8) | 99 (63.5) | 1 | |
| Often | 38 (24.4) | 33 (21.2) | 1.59 (0.87–2.89) | |
| Always | 45 (28.8) | 24 (15.4) | 2.61 (1.42–4.81) | |
| Hand washing before meals | | | | 0.001 |
| Seldom | 15 (9.6) | 15 (9.6) | 1 | |
| Regularly without soap | 125 (80.1) | 100 (64.1) | 1.27 (0.57–2.84) | |
| Regularly with soap | 16 (10.3) | 41 (26.3) | 0.33 (0.12–0.90) | |
| Hand washing after playing | | | | 0.009 |
| Seldom | 36 (23.1) | 37 (27.3) | 1 | |
| Regularly without soap | 105 (67.3) | 85 (54.5) | 1.26 (0.73–2.19) | |
| Regularly with soap | 15 (9.6) | 34 (21.8) | 0.41 (0.18–0.93) | |
| Visited public places | | | | |
| Visited hospital | 25 (16) | 28 (17.9) | 0.86 (0.47–1.60) | 0.64 |
| Visited other places‡ | 75 (48.1) | 57 (36.5) | 1.69 (1.04–2.75) | 0.033 |
| Visited public playgrounds | | | | <0.001† |
| Number visited | | | | |
| 0 | 49 (31.4) | 116 (74.4) | 1 | |
| 1 | 77 (49.4) | 33 (21.1) | 5.40 (2.91–10.03) | |
| ≥2 | 30 (19.2) | 7 (4.5) | 9.51 (3.57–25.38) | |
| Frequency of visits per week | | | | <0.001† |
| 0 | 49 (31.4) | 116 (74.4) | 1 | |

Table 1 (cont.)

| Variable | Cases (<i>n</i> = 156) | Controls (<i>n</i> = 156) | OR (95% CI) | <i>P</i> value |
|---|-------------------------|----------------------------|--------------------|----------------|
| 1-3 | 17 (10.9) | 18 (11.5) | 2.13 (0.95-4.76) | |
| 4-7 | 20 (12.8) | 13 (8.3) | 3.27 (1.29-8.24) | |
| ≥8 | 70 (44.9) | 9 (5.8) | 16.31 (6.37-41.71) | |
| Average duration of visit (min) | | | | <0.001† |
| 0 | 49 (31.4) | 116 (74.4) | 1 | |
| <15 | 5 (3.2) | 4 (2.6) | 2.88 (0.55-15.14) | |
| 15-60 | 72 (46.2) | 29 (18.6) | 5.52 (2.95-10.33) | |
| >60 | 30 (19.2) | 7 (4.5) | 11.02 (3.84-31.59) | |
| HFMD situation at home, neighbourhood and kindergarten | | | | |
| HFMD case in the same house | 7 (4.5) | 0 (0) | — | 0.008 |
| HFMD case in neighbourhood | | | | |
| No | 3 062 (98.1) | 3 112 (99.7) | 1 | |
| Yes | 58 (1.3) | 8 (0.3) | 8.25 (2.92-23.29)§ | <0.001 |
| HFMD case in the same class | 11 (37.9) | 1 (5.3) | — | 0.012 |
| HFMD case in kindergarten | 7 (24.1) | 2 (10.5) | — | 0.219 |
| Family members contact HFMD | 26 (16.7) | 0 (0) | — | <0.001 |
| Summary of contact | | | | |
| No contact | 109 (69.9) | 152 (97.4) | 1 | |
| Only direct contact | 29 (18.6) | 4 (7.6) | 13.50 (3.21-56.77) | <0.001 |
| Only indirect contact | 5 (2.2) | 0 | — | 0.0625 |
| Both direct and indirect | 13 (8.3) | 0 | — | <0.001 |

OR, Odds ratio; CI, confidence interval; s.d., standard deviation.

* The analysis included those who attended kindergarten only.

† Proportion trend test.

‡ Other places included visited other villages, relative's house, playing in the street or market, etc.

§ Rao & Scott adjustment OR by using survey analysis, as subject either case or control acted as a cluster of member of the neighbourhood or kindergarten.

Table 2. Multivariate conditional logistic regression for HFMD risk factors in Binyang County, Guangxi, China

| Variable | Crude OR (95% CI) | Adjusted OR (95% CI) | <i>P</i> value | Population fraction (95% CI) |
|---|-------------------|----------------------|----------------|------------------------------|
| Protective factor | | | | |
| Hand washing (with soap vs. without soap/seldom wash) | 0.29 (0.14-0.58) | 0.29 (0.11-0.78) | 0.013 | 0.187 (0.058-0.234)* |
| Risk factors | | | | |
| Finger sucking (often vs. seldom) | 3.29 (1.91-5.67) | 2.13 (1.05-4.32) | 0.036 | 0.275 (0.024-0.399)† |
| Visited public playground (yes vs. no) | 6.15 (3.42-11.06) | 6.03 (2.84-12.80) | <0.001 | 0.572 (0.444-0.632)† |
| Visited other places (yes vs. no) | 1.69 (1.04-2.75) | 1.03 (0.52-2.04) | 0.933 | — |
| Living near HFMD case (yes vs. no) | 8.25 (2.92-23.29) | 14.19 (3.55-56.74) | <0.001 | 0.209 (0.161-0.220)† |
| Sharing classroom with HFMD case (yes vs. no) | 11.0 (1.42-85.20) | 11.72 (1.26-109.42) | 0.031 | 0.064 (0.015-0.070)† |
| All four risk factors‡ | | | | 0.770 (0.552-0.840) |

OR, Odds ratio; CI, confidence interval.

* Prevented fraction.

† Attributable fraction.

‡ Excluding visiting other place.

number of subjects with indirect contact was small (*n* = 18) and none of the controls had only indirect contact. Therefore in multivariate analysis, both direct and indirect contact were not included in the model.

The results are summarized in Table 2. Finger sucking, hand washing before meals, exposure to public playgrounds, having HFMD in the 20 nearest neighbours and in the same class were still associated with

Table 3. *Dose-response relationship between four exposure variables related to public playgrounds and developing HFMD in Binyang County, Guangxi, China*

| Variable | Crude OR (95% CI) | Adjusted OR* (95% CI) | P value |
|---|--------------------|-----------------------|---------|
| Number of public playgrounds visited in previous 2-7 days | | | |
| 0 (reference) | | | |
| 1 | 5.40 (2.91-10.02) | 5.44 (2.45-12.10) | <0.001 |
| ≥2 | 9.51 (3.57-25.38) | 8.12 (2.57-25.68) | |
| Frequency of visits in previous 2-7 days | | | |
| 0 (reference) | | | |
| 1-3 | 2.13 (0.95-4.76) | 1.77 (0.63-4.95) | <0.001 |
| 4-7 | 3.27 (1.30-8.24) | 4.82 (1.28-18.07) | |
| ≥8 | 16.31 (6.37-41.71) | 13.58 (4.78-38.54) | |
| Average duration per exposure in previous 2-7 days (min) | | | |
| 0 (reference) | | | |
| 1-14 | 2.88 (0.55-15.15) | 1.23 (0.16-9.71) | <0.001 |
| 15-60 | 5.52 (2.95-10.33) | 6.43 (2.84-14.53) | |
| >60 | 11.02 (3.84-31.60) | 8.75 (2.47-31.08) | |
| Total exposure duration in previous 2-7 days (min) | | | |
| 0 (reference) | | | |
| 1-240 | 2.01 (0.96-4.21) | 2.13 (0.83-5.44) | <0.001 |
| 241-600 | 16.18 (4.72-55.48) | 14.53 (3.58-58.90) | |
| >600 | 16.82 (5.75-49.16) | 16.51 (4.65-58.68) | |

OR, Odds ratio; CI, confidence interval.

* Adjusted for the exposure variables shown in Table 2.

HFMD infection after adjusting for the other factors, while preschool attendance, toy sucking and visiting other places became non-significant. To clarify that visiting playgrounds was independent from visiting other places, both variables were put into the model. There was no significant interaction between finger sucking and hand washing. Living near other HFMD cases (OR 14.19, 95% CI 3.55-56.74) and sharing the same classroom at school (OR 11.72, 95% CI 1.26-109.42) posed a higher risk of being a case compared to visiting public playgrounds (OR 6.03, 95% CI 2.84-12.8).

Given that a proportion of cases exposed to playgrounds was much higher than for those living near other cases and sharing the same classroom at school, the adjusted attributable fraction of using public playgrounds turned out to be 57.2% compared to 20.9% and 6.4% in the other two strong risk factors. The adjusted attributable fraction of finger sucking was 27.5%. On the other hand, hand washing after playing was excluded from the model. Regular hand washing with soap before meals was a protective factor (OR 0.29, 95% CI 0.11-0.78) and the prevented fraction in the population was 18.7%.

We further investigated a dose-response relationship between our main variables of interest and

outcome by fitting a logistic regression model with each of the variables of interest changed to the ordinal level of exposure, one at a time, while keeping other variables the same. Results are shown in Table 3. Based on the *P* value for linear trend, the relationship between these variables and the risk of HFMD were all significant in a dose-response fashion.

DISCUSSION

As expected, having contact with a symptomatic case at home, at school and in the nearby neighbourhood were strong risk factors for HFMD. However, these exposures were not common among cases, and thus contributed relatively little to the disease epidemic. On the other hand, weaker but significant risk factors, i.e. visiting a public playground and finger sucking were very common and contributed to a high proportion of cases. Hand washing with soap before meals protected 18.7% of cases in the population.

Contact with a case was associated with increased risk of HFMD. Other studies confirm this finding, although the risk was not as high as the one found in our study [4, 15, 22]. Intra-home and neighbourhood contact was found to have a significant association with HFMD but with low attributable

fraction. More than 80% of cases in our study were from non-preschool attendance children. Moreover, given that there were strict measures taken by preschools for reducing transmission, such as preschool closure, screening at the entrance gate, the transmission mainly occurred in the community rather than preschools.

The most interesting finding was that exposure to public playgrounds had the highest attributable fraction with a dose–response relationship to HFMD. Compared to preschools, which were only attended by 16% of the study subjects, public playgrounds were visited by almost half of the children in our study. The most contagious period of HFMD is the 7 days starting from just before symptom onset, but the virus can persist in throat secretions for 1–3 weeks and can be excreted in the stool for 2–3 months [23–25]. The climate of Guangxi is warm and humid [26], conditions favourable for lengthy virus survival in the environment [27–31]. Infective children who attend public playgrounds can shed the virus particles into the environment, which further infect subsequent susceptible visitors.

Our study demonstrated that regular hand washing with soap before meals was protective against HFMD, while seldom hand washing or washing without soap was not. Soap may help to remove dirt which may contain viral particles. In addition to the possible chemical effect of soap on the virus, using soap also increases the time and thoroughness of hand washing because of the extra time needed to rinse the soap off [32, 33]. Casual hand washing is not sufficient to get rid of the organism, a fact which has been observed from studies of food poisoning and diarrhoea [34, 35]. One study has demonstrated that health education with emphasis on hand washing has a strong preventive effect on HFMD, with a dose–response relationship between hand washing score and risk of getting HFMD [14]. Our data showed that hand washing with soap before meals by children was more effective than after playing. This may relate to the fact that children have more opportunity to put their dirty hands into mouth during meal times. The population prevented fraction of hand washing before meals was only 18.7% in this study mainly because the prevalence in both cases and controls was low. Had this habit been advocated, the number of cases could have been reduced substantially.

Finger sucking was a strong independent risk factor in our study and is supported by a previous study in Tianjin [16]. The association between finger sucking

and HFMD was weaker than the other risk factors but it had a relatively high attributable fraction. Finger sucking is common in younger children [36] and the average age for spontaneous cessation of this behavior is 3.8 years [37]. The mean age of our study subjects was 2 years, which could explain the high attributable fraction observed in our study.

Despite careful selection of comparable controls for the cases and extensive visits and data collection from households, neighbourhoods and preschools of both cases and controls, this study is still limited by inherent information bias, especially recall bias. Moreover, most of the cases in this study had relatively mild symptoms. Generalization of the findings to more serious cases, which cause the real disease burden in the population, should be made with caution.

CONCLUSION

The repeated evidence of the protective effect of hand washing with soap and increased risk from finger sucking suggest a need to integrate specific preventive measure into national health education messages. The importance of public playgrounds in the transmission of HFMD reported in this study may need to be confirmed by further studies. However, because of the high attributable fraction of exposure to public playgrounds, health education could include topics which underline the precautions which need to be taken and the advice given regarding avoiding the use of public playgrounds during epidemic periods, especially when children have been getting sick.

ACKNOWLEDGEMENTS

Dr Alan Geater, Dr Chuleeporn Jiraphongsa, Dr Chaiyos Kunanusont and Dr Kittipong SaeJeng are acknowledged for help in the study design. We thank Dr Yu Ju for her help in conducting RT–PCR tests and Binyang CDC for help in data collection. We also thank all the village doctors that guided us in conducting the house and neighbourhood survey.

This research is a part of the first author's work to fulfil the requirement for a PhD degree of the International Programme for Graduate Study in Epidemiology at Prince of Songkla University. The Epidemiology Unit is partially supported by the National Science and Technology Development Agency of Thailand.

The study was supported by Guangxi Centre for Disease Prevention and Control.

DECLARATION OF INTEREST

None.

REFERENCES

- Ishimaru Y, *et al.* Outbreaks of hand, foot, and mouth disease by enterovirus 71. High incidence of complication disorders of central nervous system. *Archives of Disease in Childhood* 1980; **55**: 583–588.
- Schmidt NJ, Lennette EH, Ho HH. An apparently new enterovirus isolated from patients with disease of the central nervous system. *Journal of Infectious Diseases* 1974; **129**: 304–309.
- Gilbert GL, *et al.* Outbreak of enterovirus 71 infection in Victoria, Australia, with a high incidence of neurologic involvement. *Pediatric Infectious Disease Journal* 1988; **7**: 484–488.
- Chang LY, *et al.* Risk factors of enterovirus 71 infection and associated hand, foot, and mouth disease/herpangina in children during an epidemic in Taiwan. *Pediatrics* 2002; **109**: e88.
- Goh KT, *et al.* An outbreak of hand, foot, and mouth disease in Singapore. *Bulletin of World Health Organization* 1982; **60**: 965–969.
- Brown GC, O'Leary TP. Fluorescent antibody responses of cases and contacts of hand, foot, and mouth disease. *Infection and Immunity* 1974; **9**: 1098–1101.
- Ooi EE, *et al.* Seroepidemiology of human enterovirus 71, Singapore. *Emerging Infectious Diseases* 2002; **8**: 995–997.
- World Health Organisation. Coxsackievirus A16. *Weekly Epidemiological Record* 1981; **56**: 39–40.
- Ma E, *et al.* Effects of public health interventions in reducing transmission of hand, foot, and mouth disease. *Pediatric Infectious Disease Journal* 2011; **30**: 432–435.
- Ang LW, *et al.* Epidemiology and control of hand, foot and mouth disease in Singapore, 2001–2007. *Annals Academy of Medicine Singapore* 2009; **38**: 106–112.
- Kim KH. Enterovirus 71 infection: an experience in Korea, 2009. *Korean Journal of Pediatrics* 2010; **53**: 616–622.
- Deng T, *et al.* Spatial-temporal clusters and risk factors of hand, foot, and mouth disease at the district level in Guangdong Province, China. *PLoS ONE* 2013; **8**: e56943.
- Liu Y, *et al.* Detecting spatial-temporal clusters of HFMD from 2007 to 2011 in Shandong Province, China. *PLoS ONE* 2013; **8**: e63447.
- Ruan F, *et al.* Risk factors for hand, foot, and mouth disease and herpangina and the preventive effect of hand-washing. *Pediatrics* 2011; **127**: e898–e904.
- Park SK, *et al.* Transmission of seasonal outbreak of childhood enteroviral aseptic meningitis and hand-foot-mouth disease. *Journal of Korean Medical Science* 2010; **25**: 677–683.
- Xu WT, Gao L, Zhang Y. A case-control study on the risk factors of hand, foot and mouth disease in children in Tianjin. *Chinese Journal of Epidemiology* 2009; **30**: 100–101.
- Wu X, Fu Z, Deng G. Epidemiological characteristics of HFMD from 2008 to 2011 in Guangxi, China. *Chinese Primary Health Care* 2013; **27**: 65–66.
- Parker RA, Bregman DJ. Sample size for individually matched case-control studies. *Biometrics* 1986; **42**: 919–926.
- The Ministry of Health of China. Hand, foot and mouth disease prevention and control guideline, China (2009 version). 2009 (http://www.gov.cn/gzdt/2009-06/04/content_1332078.htm) Accessed 4 June 2009.
- Scott A. Rao-Scott corrections and their impact. Section on survey research methods, 2013, pp. 3514–3518. (<http://www.amstat.org/sections/srms/proceedings/y2007/Files/JSM2007-000874.pdf>) Accessed 24 July 2013.
- Bruzzi P, *et al.* Estimating the population attributable risk for multiple risk factors using case-control data. *American Journal of Epidemiology* 1985; **122**: 904–914.
- Guo RN, Zhang ZM, Yang F. Study on the characteristics and risk factors for hand-foot-mouth disease in Guangdong province. *Chinese Journal of Epidemiology* 2009; **30**: 530–531.
- World Health Organization. A guide to clinical management and public health response for hand, foot and mouth disease (HFMD), 2011 (<http://www.wpro.who.int/publications/docs/GuidancefortheclinicalmanagementofHFMD.pdf>) Accessed 6 January 2013
- Han J, *et al.* Long persistence of EV71 specific nucleotides in respiratory and feces samples of the patients with hand foot mouth disease after recovery. *BMC Infectious Diseases* 2010; **10**: 178.
- Li J, *et al.* Excretion of enterovirus 71 in persons infected with hand, foot and mouth disease. *Virology Journal* 2013; **10**: 31.
- Guangxi Meteorological Service Centre. Overview of climate in Guangxi (http://www.gx121.com/gx_climate_info.asp) Accessed 6 June 2013.
- Onozuka D, Hashizume M. The influence of temperature and humidity on the incidence of hand, foot, and mouth disease in Japan. *Science of the Total Environment* 2011; **410–411**: 119–125.
- Hii YL, Rocklöv J, Ng N. Short term effects of weather on hand, foot and mouth disease. *PLoS ONE* 2011; **6**: e16796.
- Ma E, *et al.* Is hand, foot and mouth disease associated with meteorological parameters? *Epidemiology and Infection* 2010; **138**: 1779–1788.
- Pirtle EC, Beran GW. Virus survival in the environment. *Revue Scientifique et Technique* 1991; **10**: 733–748.
- Bosch A, Pinto RM, Abad FX. Survival and transport of enteric viruses in the environment. In: Goyal SM, ed. *Viruses in Food*. Springer: New York, 2006, pp. 151–187.
- Savolainen-Kopra C, *et al.* Single treatment with ethanol hand rub is ineffective against human rhinovirus-hand washing with soap and water removes the virus efficiently. *Journal of Medical Virology* 2012; **84**: 543–547.
- Ejemot RI, *et al.* Hand washing for preventing diarrhoea. *Cochrane Database of Systematic Reviews* 2008; **1**: 8-11.
- Curtis V, Cairncross S. Effect of washing hands with soap on diarrhoea risk in the community: a systematic review. *Lancet Infectious Diseases* 2003; **3**: 275–281.

35. **Toshima Y, et al.** Observation of everyday hand-washing behavior of Japanese, and effects of antibacterial soap. *International Journal of Food Microbiology* 2001; **68**: 83–91.
36. **Farsi NM, Salama FS.** Sucking habits in Saudi children: prevalence, contributing factors and effects on the primary dentition. *Pediatric Dentistry* 1997; **19**: 28–33.
37. **Fukuta O, et al.** Damage to the primary dentition resulting from thumb and finger (digit) sucking. *American Society of Dentistry for Children* 1996; **63**: 403–407.