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Transmission of Seasonal Outbreak of Childhood Enteroviral Aseptic Meningitis and Hand-foot-mouth Disease

This study was conducted to evaluate the modes of transmission of aseptic meningitis (AM) and hand-foot-mouth disease (HFMD) using a case-control and a case-crossover design. We recruited 205 childhood AM and 116 HFMD cases and 170 non-enteroviral disease controls from three general hospitals in Gyeongju, Pohang, and Seoul between May and August in both 2002 and 2003. For the case-crossover design, we established the hazard and non-hazard periods as week one and week four before admission, respectively. In the case-control design, drinking water that had not been boiled, not using a water purifier, changes in water quality, and contact with AM patients were significantly associated with the risk of AM (odds ratio [OR]=2.8, 2.9, 4.6, and 10.9, respectively), while drinking water that had not been boiled, having a non-water closet toilet, changes in water quality, and contact with HFMD patients were associated with risk of HFMD (OR=3.3, 2.8, 6.9, and 5.0, respectively). In the case-crossover design, many life-style variables such as contact with AM or HFMD patients, visiting a hospital, changes in water quality, presence of a skin wound, eating out, and going shopping were significantly associated with the risk of AM (OR=18.0, 7.0, 8.0, 2.2, 22.3, and 3.0, respectively) and HFMD (OR= 9.0, 37.0, 11.0, 12.0, 37.0, and 5.0, respectively). Our findings suggest that person-to-person contact and contaminated water could be the principal modes of transmission of AM and HFMD.

Key Words : *Meningitis, Aseptic; Hand, Foot and Mouth Disease; Disease Transmission; Waterborne Infection; Enterovirus; Epidemiology*

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INTRODUCTION

Enteroviral infection is a pediatric infectious disease with a wide spectrum of clinical syndromes including mild respiratory infections, hand-foot-mouth disease (HFMD), herpangina, myocarditis, and aseptic meningitis (AM). In temperate zones, enteroviral infection has strong seasonality, being most common during summer. During the epidemic season, AM is one of the major causes of morbidity in a community, accounting for most of the acute beds occupied in the pediatric ward. More than 80% of the known etiology of AM occurs via enteroviruses. Although AM has a fairly good prognosis, children who have contracted AM are recommended to be admitted to the hospital as it is sometimes, although rarely, is accompanied by death or lethal sequelae such as encephalitis or status epilepticus (1).

It has been estimated that the attack rate of AM was 275 per 100,000 children during outbreaks in Korea (2, 3), and the nationwide incidence of aseptic meningitis among children under 15 yr of age was 3.48 per 1,000 per year (2, 3). The incidence and outbreak of AM shows cyclic fluctuations with outbreak every 3 or 4 yr, with the annual incidence in 1997 being 8.44/1,000 and that in 2000 being 0.79/1,000 (2, 3). AM outbreaks have seasonal variations since they are seasonally dependent in the temperate zone, with AM being most prevalent between May and July (4-6). AM spreads in a community within a very short period of time after detection of the index case (7).

Direct contact via the fecal-oral route with patients who have clinical or subclinical AM symptoms is the principal transmission route of AM (8, 9); however, given its strong seasonal pattern of outbreak in a community (2), direct trans-

mission is not a compatible mode of transmission in a community outbreak. Other modes of transmission including the foodborne and waterborne route should be sought during investigations of the transmission of AM (10). However, few studies have been conducted to evaluate the mode of transmission in a community except for episodic common-vehicle outbreaks. Knowledge of the major mode of transmission of AM can provide a key basis for prevention of the enteroviral infection in a community (11).

The authors assume that waterborne transmission may play an important role in community-based outbreaks (2). We also assume that AM and HFMD, the two most common enteroviral diseases, may have similar modes of transmission (5, 12). To investigate this issue, evaluation of the risk factors associated with individual patients in a community collected over a long time period is necessary. Although a case-control study is a general approach for evaluation of risk factors associated with infectious diseases, combined use of a case-crossover study will provide insight into the time-dependent exposures of an individual. Therefore, this study was conducted to investigate the mode of transmission of the two enteroviral diseases, AM and HFMD, in communities by applying case-control and case-crossover designs simultaneously.

MATERIALS AND METHODS

Case-control design

AM and HFMD cases and non-enteroviral disease (NEVD) controls were recruited from two general hospitals with 200-400 beds located in mid-sized cities in southeast Korea (Gyeongju and Pohang) and one hospital with 700 beds located in a large city (Seoul) during two seasons, 2002 and 2003. AM cases were defined as confirmed AM patients among those admitted to the hospital who met the three following criteria: 1) symptoms of meningitis such as fever and meningeal signs, 2) negative bacterial culture in the laboratory, and 3) positive test of enteroviral RNA through reverse transcription polymerase chain reaction (RT-PCR) of either cerebrospinal fluid (CSF), a fecal specimen, and/or a throat smear. HFMD cases were defined as those with a clinical syndrome of mild fever, painful oral lesions and rash, sores, or blisters on the body. NEVD controls were patients who were admitted to the hospitals with diagnoses of diseases that were unrelated to enteroviral diseases such as respiratory infectious diseases, except those from enteroviral origin, enteritis of bacterial origin, or other surgical diseases including herniotomy. All study subjects were selected as children less than 15 yr of age. Of the eligible population, we interviewed 215 AM cases, 127 HFMD cases, and 192 NEVD controls. We excluded subjects admitted during the non-seasonal outbreak (between September and April) who constituted only a small proportion (5.4%) of the AM cases. Finally, 205 AM, 116 HFMD cases and 170 NEVD controls were selected. This study was approved by the institutional review board of Dongguk University Gyeongju Hospital and informed consent was obtained from all subjects.

By structured questionnaire, we collected information regarding demographic characteristics such as age at admission and sex, as well as other environmental and lifestyle risk factors such as residential area upon examination, month of admission, boiling of drinking water, use of water purifier, drinking water supply, water used in cooking and toilet usage. We also evaluated events and/or changes in life style one month prior to hospital admission such as eating shellfish, changes in water quality including color, taste, or smell, and the presence of precipitation or floating materials in the water, as well as contact with AM, HFMD, common cold, or enteritis patients. Additionally, we collected information regarding measles-mumps-rubella (MMR) vaccination history within the previous two months to take into account the minimal incubation period following this vaccination (13) and to rule out the possibility of adverse effect of MMR vaccination since the vaccination may cause enteroviral infection or encephalitis (14, 15).

When a subject was admitted to the hospital during the study period, a research nurse recorded the date of admission to the hospital and handed the questionnaire to the subjects' parents. Within two days, the nurse collected the questionnaire and interviewed the parents for information that was not provided. We reviewed all the patients' medical charts to confirm the diagnosis in order to decrease misclassification bias.

Case-crossover design

Only AM and HFMD cases were selected for the case-crossover design (N=205, 116, respectively). Information collected for the case-crossover design was primarily designed to delineate the subject's unusual events in detail and/or changes in life style at weekly intervals for the one month prior to admission. Possible indicators for contact with clinical or subclinical AM or HFMD patients were contact with AM and HFMD cases and being admitted to or visiting a hospital. Possible indicators for virus-contaminated drinking water were changes in color, taste, or smell, and the presence of precipitates or floating materials in the water. Possible indicators for direct skin or mucosal contact with virus-contaminated water were use of public saunas and swimming pool and presence of a skin wound. Possible indicators for drinking water in places other than home were eating out, going shopping, going for a picnic, and going to amusement parks. Although the incubation period of enterovirus infection is usually between the 3rd and 7th day after contact (16), some studies demonstrated a longer incubation period for AM of up to 15 days (17). Therefore, the first week (1-7 days) prior to admission was established as the hazard period and the

fourth week (22-28 days) prior to admission was considered to be the non-hazard period. Subjects were classified into two categories that were exposed to any modes of transmission during the hazard and non-hazard period.

Statistical analysis

A chi-square test and Fisher's exact test were used to evaluate the group differences between cases and controls. Missing data under 5% of frequency were imputed to the code of reference level in a variable that shifts risk of AM or HFMD towards the null hypothesis. To determine the AM or HFMD risk associated with each mode of transmission in the case-control design, we estimated the adjusted odds ratios (ORs) and corresponding 95% confidence intervals (CIs) by unconditional logistic regression analysis adjusted for age, residential area at examination, and month of admission. We also estimated the risk of AM or HFMD in the case-crossover design, and compared the exposure status during the hazard and non-hazard periods using the ORs (95% CIs) via the conditional logistic regression model. All analyses were conducted by SAS 9.1.

RESULTS

Age, residential area at examination, month of admission among the AM cases, and the age and residential area among the HFMD cases and NEVD controls were significantly different (Table 1).

Case-control design

When compared to the controls, subjects who did not boil drinking water and did not use a water purifier had an increased risk for AM (OR=2.8 [95% CI=1.4-5.6] and 2.9 [95% CI=1.5-5.5], respectively) (Table 2). Subjects who reported changes in color, taste, or smell and the presence of floating particles in the water also had significantly higher risks for AM (OR=4.6 [95% CI=1.4-15.1]). Contact with an AM patient 1 month prior to admission was associated with a significantly higher risk for AM (OR=10.9 [95% CI=2.0-52.0]). Risk of HFMD was associated with not boiling drinking water and changes in water quality (OR=3.3 [95% CI=1.6-7.0] and OR=6.9 [95% CI=2.2-22.2], respectively). Toilet status (non-water closet toilet) and contact with HFMD patients were significant risk factors for HFMD (OR=2.8 [95% CI=1.1-6.7] and OR=5.0 [95% CI=1.4-17.7], respectively). However, other factors were not associated with the risk of AM or HFMD.

Case-crossover design

The results of the case-crossover study are shown in Table 3. Of the possible indicators for contact with clinical or subclinical AM or HFMD patients, contact with AM patients was associated with an increased AM risk (OR=18.0, [95% CI=2.4-134.5]), while contact with HFMD patients was associated with an increased risk for HFMD (OR=9.0, [95% CI=1.1-71.0]). Being admitted to or visiting a hospital was associated with both AM and HFMD risks (OR=7.0, [95% CI=

Table 1. Selected characteristics of AM† cases, HFMD‡ cases and NEVD* controls

Characteristics	NEVD* controls (n=170)	AM† cases (n=205)	*P* value§	HFMD‡ cases (n=116)	*P* value‖
Age (yr)					
0-3	95 (55.9)	38 (18.5)	<0.001	62 (53.4)	<0.001
4-6	36 (21.2)	51 (24.9)		24 (20.7)	
7-12	23 (13.5)	51 (24.9)		13 (11.2)	
13-15	16 (9.4)	65 (31.7)		17 (14.7)	
Sex					
Male	105 (61.8)	136 (66.3)	0.35	66 (56.9)	0.12
Female	65 (38.2)	69 (33.7)		50 (43.1)	
Residential area of examination					
City 1 (mid-sized city)	130 (76.5)	135 (65.9)	<0.001	115 (53.7)	<0.001
City 2 (mid-sized city)	29 (17.1)	30 (14.6)		98 (45.8)	
City 3 (big city)	11 (6.4)	40 (19.5)		1 (0.5)	
Month of admission					
May	34 (20.0)	83 (40.5)	<0.001	43 (37.1)	0.88
June	31 (18.2)	76 (37.1)		48 (41.4)	
July	59 (34.7)	30 (14.6)		17 (14.7)	
August	46 (27.1)	16 (7.8)		8 (6.9)	

*Non-enteroviral diseases (NEVD) controls unrelated to enteroviral diseases, such as respiratory infectious diseases and enteritis of bacterial origin, and other surgical diseases; †Aseptic meningitis (AM); ‡Hand-foot-mouth disease (HFMD) controls; §*P* values for the difference between AM cases and NEVD controls; ‖*P* values for the difference between HFMD cases and NEVD controls.

Table 2. The association between the mode of transmission and risk of AM† or HFMD‡ in case-control design

Characteristics within 1 month prior to admission	NEVD* controls No. (%)	AM† cases No. (%)	OR (95% CI)§,‖	HFMD‡ cases No. (%)	OR (95% CI)§,¶
Boiling of drinking water					
Always	131 (77.1)	113 (55.1)	1.00	65 (56.0)	1.00
Sometimes or never	39 (22.9)	92 (44.9)	2.83 (1.44-5.59)	51 (44.0)	3.34 (1.59-6.99)
Use of water purifier					
Yes	84 (49.4)	96 (46.8)	1.00	57 (49.1)	1.00
No	86 (50.6)	109 (53.2)	2.90 (1.52-5.54)	59 (50.9)	1.47 (0.72-2.99)
Drinking water supply					
Tap water	141 (82.9)	160 (78.1)	1.00	91 (78.5)	1.00
Water from well or underground; commercial mineral water	29 (17.1)	45 (21.9)	0.85 (0.30-2.42)	25 (21.5)	0.67 (0.22-2.06)
Water used in cooking					
Tap water	148 (87.1)	180 (87.8)	1.00	102 (87.9)	1.00
Water from well or underground; commercial mineral water	22 (12.9)	25 (12.2)	0.71 (0.22-2.25)	14 (12.1)	1.32 (0.38-4.56)
Type of toilet					
Flush, individual, and inside the house	155 (91.2)	189 (92.2)	1.00	98 (84.5)	1.00
Traditional, communal, or outside the house	15 (8.8)	16 (7.8)	0.81 (0.34-1.97)	18 (12.5)	2.77 (1.14-6.74)
Eating shellfish					
No	151 (88.8)	182 (88.8)	1.00	100 (86.2)	1.00
Yes	19 (11.1)	23 (11.2)	0.50 (0.23-1.09)	16 (13.8)	1.05 (0.42-2.65)
Changes in water quality					
No	165 (97.1)	187 (91.2)	1.00	100 (86.2)	1.00
Yes	5 (2.9)	18 (8.8)	4.56 (1.38-15.09)	16 (13.8)	6.93 (2.17-22.15)
Contact with AM patients					
No	168 (98.8)	182 (88.8)	1.00	115 (99.1)	1.00
Yes	2 (1.2)	23 (11.2)	10.93 (2.04-52.00)	1 (0.9)	0.87 (0.04-18.18)
Contact with HFMD patients					
No	166 (97.7)	199 (97.1)	1.00	102 (87.9)	1.00
Yes	4 (2.3)	6 (2.9)	1.11 (0.24-5.20)	14 (12.1)	4.96 (1.39-17.67)
Contact with URI** patients					
No	158 (92.9)	191 (93.2)	1.00	102 (87.9)	1.00
Yes	14 (12.1)	14 (6.8)	1.33 (0.49-3.61)	14 (12.1)	1.52 (0.52-4.38)
MMR†† vaccination within past 2 months					
No	165 (97.1)	199 (97.1)	1.00	108 (93.1)	1.00
Yes	5 (2.9)	6 (2.9)	1.15 (0.26-5.13)	8 (6.9)	3.35 (0.90-12.44)

OR (95% CI) of contact with viral enteritis patients in the previous month was not estimated because there was no control subjects with viral enteritis.
*Non-enteroviral diseases (NEVD) controls unrelated to enteroviral diseases, such as respiratory infectious diseases and enteritis of bacterial origin, and other surgical diseases; †Aseptic meningitis (AM); ‡Hand-foot-mouth disease (HFMD) controls; §Adjusted for age, residential area at examination, month of admission, and all variables listed in Table 2; ‖ORs (95% CIs) for AM risk relative to NEVD controls; ¶ORs (95% CIs) for HFM risk relative to NEVD controls; **Upper respiratory infections; ††Measles-mumps-rubella.

3.0-16.5] and OR=37.0, [95% CI=5.1-269.5], respectively). Changes in water as a possible indicator for virus-contaminated drinking water was related to a significantly increased risk for AM and HFMD (OR=8.0, [95% CI=1.1-64.0] and OR=11.0, [95% CI=1.2-72.9], respectively). Of the possible indicators for direct skin contact with virus-contaminated water, having a skin wound was associated with AM as well as HFMD risk (OR=2.2, [95% CI=1.1-4.9] and OR=12.0, [95% CI=1.6-92.3], respectively). Of the possible indicators for drinking water in places other than home, eating out and going shopping were associated with both AM and HFMD risks (OR=22.3, [95% CI=7.0-71.0] and OR=3.0, [95% CI=1.0-9.3] for AM risk; OR=37.0, [95% CI=5.1-269.5] and OR=5.0, [95% CI=1.9-13.1] for HFMD risk, respectively).

DISCUSSION

In this case-control and case-crossover design for AM and HFMD, modes of transmission associated with an increased risk were non-boiling of drinking water, change in water quality within one month prior to admission, contact with pati-

Table 3. The association between mode of transmission and risk of AM* and HFMD† using a conditional logistic regression model in a case-crossover design

Possible indicators	Life-style changes between hazard period (1 week prior to admission) and non-hazard period (4 weeks prior to admission)	AM* cases			HFMD† cases		
		No.‡ (a§/b‖)	OR (95% CI)	*P* value	No.‡ (a§/b‖)	OR (95% CI)	*P* value
Contact with clinical or subclinical AM* or HFMD† patients	Contact with AM[1] cases	205 (18/1)	18.0 (2.4-134.5)	0.01	116 (0/0)	–	
	Contact with HFMD[2] cases	205 (5/0)	–		116 (9/1)	9.00 (1.1-71.0)	0.001
	Being admitted to or having visited a hospital	205 (42/6)	7.0 (3.0-16.5)	0.001	116 (37/1)	36.99 (5.1-269.5)	0.001
Drinking contaminated water	Changes in water quality	177 (8/1)	8.0 (1.1-64.0)	0.04	101 (11/1)	11.0 (1.2-72.9)	0.03
Direct skin contact with contaminated water	Use of public saunas	205 (5/1)	5.0 (0.6-42.8)	0.14	116 (13/7)	1.9 (0.7-4.7)	0.19
	Swimming in a pool	205 (9/4)	2.3 (0.7-7.3)	0.18	116 (3/1)	3.0 (0.3-28.8)	0.34
	Presence of a skin wound	205 (20/9)	2.2 (1.1-4.9)	0.04	116 (12/1)	12.00 (1.56-92.3)	0.02
Drinking water in places other than home	Eating out	205 (67/3)	22.3 (7.0-71.0)	0.00	116 (37/1)	37.0 (5.1-269.5)	0.001
	Going shopping and eating	205 (12/4)	3.0 (1.0-9.3)	0.05	116 (25/5)	5.0 (1.9-13.1)	0.01

OR (95% CI) of the use of a purifier was not estimated because we surveyed monthly changes and not the weekly changes.
*Aseptic meningitis (AM); †Hand-foot-mouth diseases (HFMD); ‡Total number of cases for analysis; §Subjects exposed to risk factor in the hazard period only (1 week prior to admission); ‖Subjects exposed to risk factor in the hazard period only (4 weeks prior to admission).

ents with the same disease (AM or HFMD), drinking water in places other than home (eating out and going shopping), and direct skin contact with potentially contaminated water such as having a skin wound. Not using a water purifier was only associated with the risk of AM, whereas the use of unsanitary toilets was associated with HFMD risk.

Studies have shown that drinking unpurified water was a cause of AM outbreak (10, 18, 19). Our findings of an increased risk among subjects who did not use a water purifier and who did boil drinking water strongly suggest that AM infection in a community is related to drinking water. Furthermore, increased risk in subjects who experienced changes in drinking water within one week prior to admission directly implicated potentially contaminated water as the principal mode of transmission for both AM and HFMD. In some studies, enteroviruses such as Coxsackie virus and adenovirus have been isolated from both water supply facilities and tap water (20, 21). Although our results could not offer direct evidence of enterovirus-contaminated water contact, it is still possible that the virus-contamination of drinking water may also be the mode of transmission for the outbreak of AM and HFMD.

Our study shows that contact with an AM or HFMD patients is a strong risk factor with very high ORs when compared to water-related risk factors. However, the population attributable risk of direct contact should be much lower than that of the waterborne sources because the proportion of children with contact history is lower than 10% of the total cases among study subjects. Considering that the incubation period of enteroviral diseases is one or two weeks, infection through common vehicle exposure is a more plausible explanation of the primary mode of transmission of the community cases during the outbreak season. In addition, our study supports the results of previous studies that contact with potentially contaminated water, such as direct skin or mucosal contact through bathing and swimming, and environments of unsafe water, could be other modes of AM transmission, in addition to direct contact with patients (17, 22-24).

The case-crossover design, developed by Maclure (25), requires information only from cases (26). This design has the advantage of enabling adjustment of confounding factors since the cases themselves serve as the controls during the non-hazard period (27). This design has proven useful for the identification of time-dependent risk factors of diseases or health effects within a short time frame from exposure to outcome (27, 28). In our case-crossover design, factors possibly related to direct contact with patients infected by enterovirus and drinking or skin contact with virus contaminated water were significant or marginally significant. In addition, a recent study reported that the case-crossover design was useful for confirming the risk of acute adverse events of aseptic meningitis after receiving MMR vaccination. In this study, the results of the case-crossover study were similar to those of the case-control study (13).

We included the MMR vaccination history as a risk factor of AM or HFMD due to differential classification of AM or HFMD by enteroviral infections and meningitis or encephalitis based on the adverse effects of MMR vaccination (13-15). MMR vaccination history was not associated with AM or HFMD risks in our results; thus, we could not rule out the possibility of AM development related to MMR vaccination.

In this study, the presence of contact history with patients of AM or HFMD was associated with a highly increased risk of AM and HFMD. We collected additional information regarding substitutes of person-to-person contact, such as the number of family members, number of rooms in the residence, number of rooms per one person to measure the spatial den-

sity, and the number of children taken to nursery care among pre-schoolers. However, none of these variables were associated with the risk of AM and HFMD.

This study had some limitations. The number of cases and controls between small city/county and large city was significantly different, which suggests that there are differences in the quality and quantity of the water supply and socioeconomic conditions among the three areas. However, those conditions were determined by the geographic location of the study subjects and differed among areas. Therefore, we included residential area at examination as a covariate to reduce information bias. Information regarding the frequency and quantity of water consumption was not collected. Although changes in water quality consisted of many variables such as changes in color, taste, and smell, and the presence of precipitation or floating materials in the water, we did not collect specific data regarding water quality measurement. Thus, our results may be subject to misclassification bias. Our definition of HFMD cases and NEVD controls was defined according to clinical symptoms and may therefore have lacked specificity since we cannot guarantee that all cases were of enteroviral origin and that all controls were attributed to non-enteroviral origin. However, this bias can act towards the null and underestimate the effect size.

Nevertheless, this study has several strengths. Misclassification bias was minimized since AM cases were defined by serological or virological evidence of infection rather than by clinical diagnosis. We also selected a group of HFMD cases who had equal opportunity for exposure to enteroviruses. Additionally, the results from both our case-control and case-crossover designs were consistent. Our study subjects represent most of the AM cases in a community during outbreak season. Our results regarding risk factors suggest water contamination as a common mode of disease transmission in community cases.

Our findings demonstrate that viral contamination of water could be a potential risk factor for AM and HFMD, even though person-to-person contact history is the most important risk factor. Therefore, the practice of boiling drinking water and use of a water purifier at home are considered to be effective means of protecting against AM and HFMD. Maintenance of a high level of sanitation of public saunas and swimming pools and avoidance of the use of such places for those who have skin wounds is recommended. A nationwide surveillance and quality control of drinking water sources are also needed. An effective water control strategy for AM and HFMD could reduce childhood morbidity (29) as well as national medical expense (1).

REFERENCES

1. Nwachuku N, Gerba CP. *Health risks of enteric viral infections in children. Rev Environ Contam Toxicol 2006; 186: 1-56.*
2. Cheong HK, Park SK, Ki M, Lee K. *Six year national trend of childhood aseptic meningitis incidence in Korea, 1996-2001. Korean J Epidemiol 2008; 30: 252-62.*
3. Park SK, Cheong HK, Ki M, Son YM, Kim H. *Assessment of the availability of health insurance data for epidemiologic study of childhood aseptic meningitis. Korean J Prev Med 2003; 36: 349-58.*
4. Jee Y, Cheon D, Choi W, Ahn J, Kim K, Chung Y, Lee J, Lee K, Noh H, Park K, Lee S, Kim S, Cho K, Kim E, Jung J, Yoon J, Cho H. *Updates on enterovirus surveillance in Korea. Infect Chemother 2004; 36: 294-303.*
5. Lee YA, Oh SH, Hong SJ, Kim YH, Moon HN, Hong CY. *Hand, foot and mouth disease associated with the aseptic meningitis in Seoul, 1990. J Korean Pediatr Soc 1993; 36: 842-9.*
6. Oh SH, Lee MS, Kang JH, Kim CH, Park CY, Sohn YM, Lee HJ, Chun CS, Shin SM. *Report of nationwide epidemiology of aseptic meningitis outbreak in 1993 in Korea. J Korean Pediatr Soc 1996; 39: 42-52.*
7. You JH, Lee KY, Lee HS, Hong JH, Lee MH, Lee BC. *Epidemiologic study of aseptic meningitis in Daejeon, Korea (1987 through 2003). Korean J Pediatr 2004; 47: 1181-5.*
8. Takao S, Komazawa Y, Fukuda S, Shimazu Y, Noda M, Tokumoto S. *Duration of echovirus 30 excretion in stools from patients with aseptic meningitis. Jpn J Infect Dis 2000; 53: 132-3.*
9. Staggs W, Gorsuch S. *Enterovirus season and aseptic meningitis clusters: it's that time of year. Indiana Epidemiology Newsletter 2007. Available at http://www.in.gov/isdh/files/Sep07newsletter.pdf [accessed 1 Sep 2009].*
10. Amvrosieva TV, Titov LP, Mulders M, Hovi T, Dyakonova OV, Votyakov VI, Kvacheva ZB, Eremin VF, Sharko RM, Orlova SV, Kazinets ON, Bogush ZF. *Viral water contamination as the cause of aseptic meningitis outbreak in Belarus. Cent Eur J Public Health 2001; 9: 154-7.*
11. Kasper DL, Braunwald E, Fauci AS, Hauser SL, Longo DL, Jameson JL. *Harrison's principle of internal medicine, 17th ed. New York, NY: McGraw-Hill, 2008; 1208-13.*
12. Fujimoto T, Chikahira M, Yoshida S, Ebira H, Hasegawa A, Totsuka A, Nishio O. *Outbreak of central nervous system disease associated with hand, foot, and mouth disease in Japan during the summer of 2000: detection and molecular epidemiology of enterovirus 71. Microbiol Immunol 2002; 46: 621-7.*
13. Ki M, Park T, Yi SG, Oh JK, Choi B. *Risk analysis of aseptic meningitis after measles-mumps-rubella vaccination in Korean children by using a case-crossover design. Am J Epidemiol 2003; 157: 158-65.*
14. Bitnun A, Shannon P, Durward A, Rota PA, Bellini WJ, Graham C, Wang E, Ford-Jones EL, Cox P, Becker L, Fearon M, Petric M, Tellier R. *Measles inclusion-body encephalitis caused by the vaccine strain of measles virus. Clin Infect Dis 1999; 29: 855-61.*
15. Nakayama T, Onoda K. *Vaccine adverse events reported in postmarketing study of the Kitasato Institute from 1994 to 2004. Vaccine 2007; 25: 570-6.*
16. National Center for Infectious Diseases, Center for Disease Control and Prevention. *Viral ("aseptic") meningitis FAQs. Available at http://www.cdc.gov/meningitis/viral/viral-faqs.htm [accessed 31 October 2008].*

17. Faustini A, Fano V, Muscillo M, Zaniratti S, La Rosa G, Tribuzi L, Perucci CA. *An outbreak of aseptic meningitis due to echovirus 30 associated with attending school and swimming in pools*. *Int J Infect Dis 2006; 10: 291-7*.
18. Amvrosieva TV, Paklonskaya NV, Biazruchka AA, Kazinetz ON, Bohush ZF, Fisenko EG. *Enteroviral infection outbreak in the Republic of Belarus: principal characteristics and phylogenetic analysis of etiological agents*. *Cent Eur J Public Health 2006; 14: 67-73*.
19. Kim H, Cheong HK, Park SK. Bae GR. *Drinking water turbidity and aseptic meningitis in children in an urban community in Korea*. *Epidemiology 2003; 14: S110*.
20. Lee SH, Kim SJ. *Detection of infectious enteroviruses and adenoviruses in tap water in urban areas in Korea*. *Water Res 2002; 36: 248-56*.
21. Cho HB, Lee SH, Cho JC, Kim SJ. *Detection of adenoviruses and enteroviruses in tap water and river water by reverse transcription multiplex PCR*. *Can J Microbiol 2000; 46: 417-24*.
22. Hauri AM, Schimmelpfennig M, Walter-Domes M, Letz A, Diedrich S, Lopez-Pila J, Schreier E. *An outbreak of viral meningitis associated with a public swimming pond*. *Epidemiol Infec 2005; 133: 291-8*.
23. Centers for Disease Control and Prevention. *Aseptic meningitis outbreak associated with echovirus 9 among recreational vehicle campers-Connecticut, 2003*. *MMWR Morb Mortal Wkly Rep 2004; 53: 710-3*.
24. Centers for Disease Control and Prevention (CDC). *Outbreak of aseptic meningitis associated with multiple enterovirus serotypes-Romania, 1999*. *MMWR Morb Mortal Wkly Rep 2000; 49: 669-71*.
25. Maclure M. *The case-crossover design: a method for studying transient effects on the risk of acute events*. *Am J Epidemiol 1991; 133: 144-53*.
26. Navidi W. *Bidirectional case-crossover designs for exposures with time trends*. *Biometrics 1998; 54: 596-605*.
27. Lee JT, Kim H, Schwartz J. *Bidirectional case-crossover studies of air pollution: bias from skewed and incomplete waves*. *Environ Health Perspect 2000; 108: 1107-11*.
28. Rothman KJ, Greenland S, Timothy L, Lash TL. *Modern epidemiology, 3rd ed*. *Philadelphia, PA: Lippincott Williams & Wilkins, 2008, p125-6*.
29. Oh SH. *Aseptic meningitis*. *J Korean Med Assoc 2003; 46: 722-8*.