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An Investigation of Risk Factors in a Hepatitis A Outbreak in a College in Tamshui

1. Introduction

A suspected hepatitis A outbreak in a junior college in Tamshui was reported on 27 May 1995. To understand the situation and to identify both the sources and mode of infection for the control of the outbreak, a team was sent to the college for investigation on 29 May. The first case of hepatitis A occurred on 14 March. The number of cases had increased by the end of April. The junior college has both the five-year and the two-year programs with 5,000 students in the day classes and 1,000 in the night classes. Junior students of the five-year program usually stay in dormitories: whereas senior students of the five-year programs and students of the two-year program stay in rented rooms off campus. There is a cafeteria in the college supplying three meals to students by 19 cooks. Tap water is used for cooking, and underground water for washing. Initial interview with the health care staff of the college and visits to the rented rooms of the students showed that there was a significant under-reporting of cases; and that most cases were senior students and no cases were found among the junior students. Most junior students had their meals in school: whereas, most senior students ate outside. None of the cases went abroad, visited mountain areas, or attended wedding parties or any large scale garden parties during this period. Therefore, a common community-oriented source of infection was suspected and an epidemiological investigation was carried out soon.

2. Materials and Method

I. Collection of data:

The case-control method was used in the investigation. A structured questionnaire was developed and pre-tested. For pre-testing, 15 some hepatitis A students treated at the Tamshui Mackay Memorial Hospital were asked to fill out the draft questionnaire and corrections were made thereafter. Data were collected in June and July 1995 when students were mass inoculated with immuno-globulin or taking the make-up examination at school. Items contained in the questionnaire included: basic information of the case, place of residence, drinking water at the place of residence, symptoms and time of onset, hospital care, inoculation with immuno-globulin, and exposure to public eating places outside school. All 28 public eating places around the college were mapped and numbered. They were photographed and shown to the students to avoid any recall bias. The geographical location of these eating places is shown in Figure 1.

2 Serological examinations:

Serum specimens were collected by the Taipei County Health Bureau and the Tamshui Health Station from 1 ,923 individuals: some students who did not know if they were infected with hepatitis A but came forward for immunoglobulin inoculation, cooks of the school cafeteria, cooks and assistants of the public eating places, and some community residents across the college. The specimens were sent to the National Institute of Preventive Medicine for laboratory testings for 1gM anti-HAV and total anti-HAV by the Solid Phase Enzymeimmunoassay HEPAVASE and HEPAVASE A (General Biologicals Corporation, ROC).

3. Definition of case:

An individual who was found IgM anti-HAV positive in the serological examination either by the National Institute of Preventive Medicine or the hospital was defined as a lab-confirmed case.

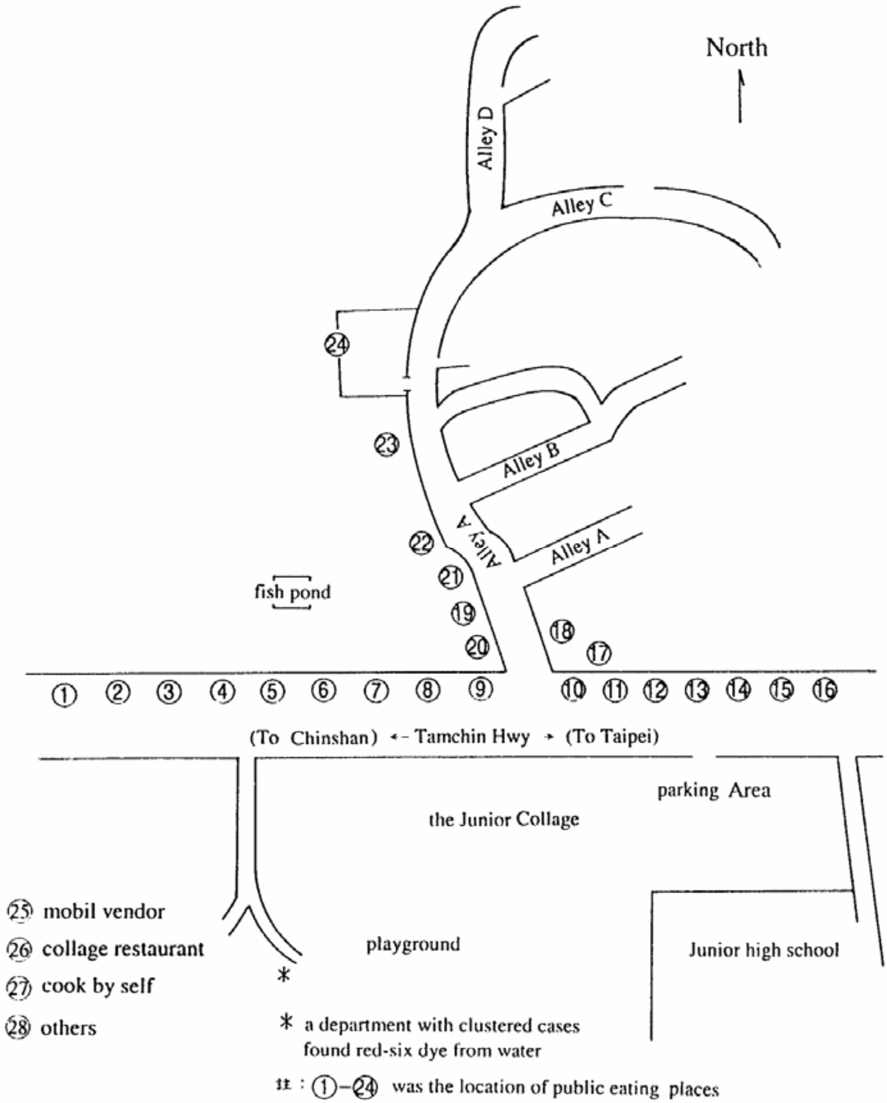
An individual who was found anti-HAV total antibody negative and also IgM anti-HAV negative in the laboratory testing by the National Institute of Preventive Medicine or the hospital was defined as a lab-confirmed non-case and placed in the control group.

4 Methods of statistical analysis:

Data were stored with Lotus Approach 3.0 and analyzed with S-plus and SAS (statistical analysis system, v604). As blood specimens were collected only from some of the students who had been questionnaire-interviewed, only those confirmed by laboratory testings for hepatitis A were used by the present study as either the lab-confirmed cases or the lab-conformed non-cases. Those who were not confirmed by laboratory testings were grouped into post-classification cases and post-classification non- cases by discriminant analysis based upon the discriminant criteria derived from the symptoms given by the students in the questionnaires.

An individual's basic information including age, class, place of residence, symptoms and time of onset, was processed with the frequency analysis method and then tested with χ^2-test for risk factors such as the place of residence, source of drinking water

Figure 1. Geographical Location of 28 Public Eating Places Around College



and exposure to the 28 public eating places, of hepatitis A infection and their relationship with the inoculation of immuno-globulin. Finally, considering the likelihood of exposure to multiple factors and to control mutual interference of factors, the stepwise logistic regression method was used in the analysis. Though all cases were assigned to two groups: the lab-confirmed cases and the lab-confirmed non-cases, and the post- classification cases and the post-classification non-cases, in the analysis, it was found that the relationship between infection and exposure was relatively constant in the two groups, indicating that though cases were grouped based on symptoms, the grouping of cases and non-cases in such a way could reflect the risks of exposure. However, the number of samples in both the lab-confirmed cases and non-cases was too small and the standard error too large, all cases were used for analysis in the stepwise logistic regression analysis. For single variables, to show the specificity of data, both lab- confirmed cases and non-cases were used.

The antibody prevalence rates were derived from:

a. hepatitis A antibody prevalence = [anti-HAV(+) and IgM anti-HAV(－)]/ total No.

b. attack rate = (No. of IgM anti-HAV(+)/[total No. － No. of anti-HAV (+) and 1gM anti-HAV (－)]

c. susceptible rate = [total No. － No. of anti-HAV(+) and 1gM anti-HAV(－)]/ total No

5. Environmental Examination

Environmental specimens (including specimens of tap water and underground water) were collected by the Taipei County Health Bureau and the Tamshui Health Station from the college, students' living areas with more cases, and the public eating places for laboratory testings by the County Health Bureau for the number of bacteria, coliform and E. coli.

6. Testing for underground water contamination:

To confirm whether the underground water was contaminated by feces, four houses around the college with more hepatitis A cases and three control houses without cases were selected. 3 kg of Red #6 was dropped in the toilet of each house after a control blank for comparing changes in color was collected from the toilet. Specimens were collected in four consecutive days and sent to the County Health Bureau for the testings of any fluorescent red to decide if the underground water was contaminated by feces

4. Results

1. Classification of subjects:

596 copies of the questionnaire were returned. Of them, 228 persons had their blood specimens taken for laboratory testings. Of them, 63 were confirmed hepatitis A positive after the testings, and 165 negative. Of the rest 368 persons from whom no blood specimens were collected for laboratory testings, 63 were placed in the case group, and 305 in the non-case group.

2. Analysis of personal information:

1) Characteristics of subjects:

(1) Age, class and place of residence

The average age of the lab-confirmed cases, non-cases and the post-classification cases and non-cases was 19 years. Cases were evenly distributed in different classes, no clustering of cases was noted. In terms of residence, living off campus was found to be significantly related to the hepatitis A infection (OR=2.43, $p<0.005$) (Table 1).

Table 1. Living Off-Campus and Hepatitis A Infection

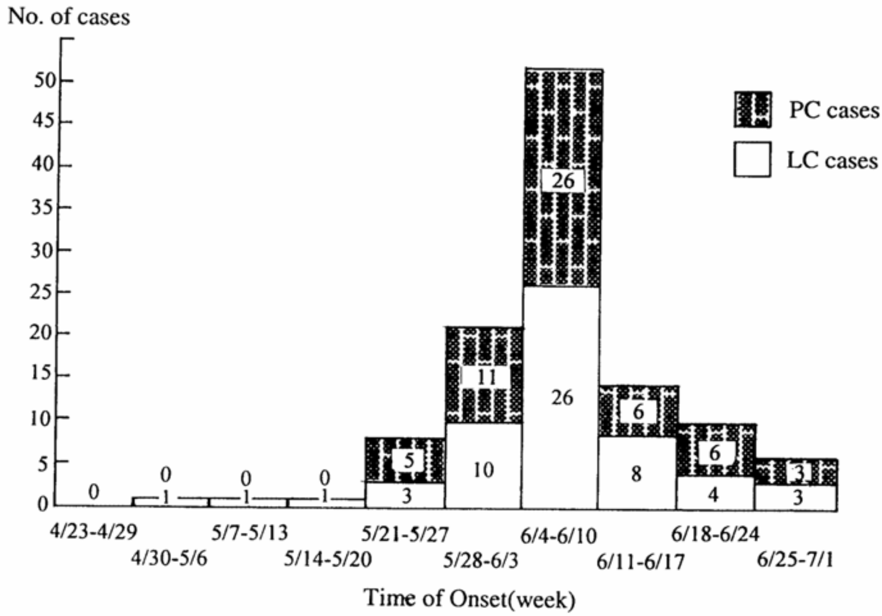
	Around College	Not Around College	Not Available	OR	95% CI	p-value
LC cases	39	22	2	2.43	1.27-4.69	0.038
LC non-cases	67	92	6			
PC cases	39	21	3	3.85	2.07-7.22	0.000
PC non-cases	93	193	19			

Note: LC cases for lab-confirmed cases; LC non-cases for lab-confirmed non-cases; PC cases for post-classification cases; and, PC non-cases for post-classification non-cases.

(2) Distribution of symptoms

The early symptoms of the lab-confirmed cases were: fever (38%), abdominal discomfort (28.6%), tiredness (19.0%), anorexia (19.0%), brown urine (63.4%), diarrhea (3.2%), sleeplessness (3.2%). disorders of liver functions (3.2%), nausea (1.6%) and jaundice (1.6%). The distribution of symptoms of the post-classification cases was similar to that of the lab-confirmed cases. Of the lab-confirmed cases, three (5.3%) developed symptoms before 20 May. 10 (17.5%) between 20 and 31 May, 35 (61.4%) between I and 15 June. and 9 (15.8%) after 15 June. Of the post-classification cases, none became ill before 20 May. 12 (21.2%) became ill between 20 and 31 May, 32 (56.1%) between I and 15 June, and II (19.3%) after 15 June. The epidemiological curve is shown in Figure 2. Of the 63 post-examination cases, 31 (49.2%) were taken to the hospital for care.

Figure 2. Epidemiological Curve of Hepatitis A (N=114, April-June 1995)



2) Analysis of risk factors related to the hepatitis A infection:

(I) Use of drinking water

In terms of the Sources of drinking water, the hepatitis A infection was found to he positively related to the underground water (OR=2.10, p=0.013), and negatively related to the tap water (OR=0 44. p=0.006) The use of underground water for drinking, drinking from fountain, drinking after boiling, washing and toilet was found not related to the hepatitis A infection. The use of tap water for drinking after boiling was the only factor that was found negatively related to the hepatitis A infection (OR=0.4. p=0.012) (Tables 2 and 3). When multiple logistic regression was applied to analyze the sources of drinking water, it was found that after other sources of drinking water were controlled, the use of any drinking water was found not related to the hepatitis A infection (p>0.05) (Table 4).

Table 2. Drinking Water and Hepatitis A Infection (N=596)

Using underground water	Yes	No	OR	95% CI	χ^2	p-value
LC cases	32	31	2.10	1.11-3.98	6.14	0.013*
LC non-cases	53	108				
PC cases	33	30	3.09	1.71-5.60	15.50	0.000*
PC non-cases	79	222				
Using tap water						
LC cases	31	32	0.44	0.23-0.83	7.6	0.006*
LC non-cases	111	50				
PC cases	43	20	0.64	0.34-1.21	1.74	0.138
PC non-cases	232	69				
Using mineral water						
LC cases	12	51	1.17	0.51-2.63	0.16	0.689
LC non-cases	27	134				
PC cases	15	48	1.20	0.60-2.39	0.16	0.691
PC non-cases	62	139				

* $p<0.05$

(2) Exposure to public eating places

By single-variate analysis to compare difference between the lab-confirmed cases and the lab-confirmed non-cases in their exposure to public eating places, it was found that eating places Nos. 4. 5, 11, 14, 15, 17, 18, 21, 22, 23, 24, 25 and 28 were significantly related to the infection (Table 5). Again, by χ^2-test for trend, it was found that eating places Nos. 4, 5, 11, 13, 15, 17, 18, 21, 22, 23, 24, 26 and 28 were significantly related to the infection (Table 6). That is, the more frequently one visited a particular eating place, the chances of being infected with hepatitis A were higher. Further, by multivariate analysis to study the relationship between hepatitis A infection and exposure to public eating places, it was found that only eating places Nos. 5,11 and 23 were positively related (Table 7).

Table 3. Use of Drinking Water and Hepatitis A Infection (N=596)

1. Underground Water						
Drinking fountain	Yes	No	OR	95% CI	χ^2	p-value
LC cases	17	44	1.87	0.88-3.97	3.19	0.074*
LC non-cases	27	131				
PC cases	17	45	2.42	1.20-4.85	6.40	0.011*
PC non-case	40	256				
Washing and toilet						
LC cases	12	49	1.37	0.53-3.13	0.64	0.424
LC non-cases	24	134				
PC cases	13	49	2.88	1.29-6.53	7.20	0.007*
PC non-cases	25	271				
Others						
LC cases	5	56	1.47	0.41-5.07	0.44	0.507
LC non-cases	9	148				
PC cases	7	55	3.30	1.10-9.71	4.67	0.022*
PC non-cases	11	285				
2. Tap Water						
Boiled						
LC cases	11	50	0.40	0.18-0.87	6.28	0.012*
LC non-cases	53	96				
PC cases	16	44	0.46	0.24-0.89	5.56	0.018*
PC non-cases	125	158				

* $p<0.05$

Table 4. Multivariate Analysis of Use of Drinking Water (N=228)

	Coefficient	SE	χ^2	p-value
Intercept	0.8035	0.4001	4.0341	0.0446
Underground water	0 4259	0.3833	1.2347	0.2665
Tap water	−0 5681	0.3825	2.2062	0.1375
Mineral water	0.1381	0 4025	0 1178	0.7314

Table 5. Relationship between Public Eating Places and Hepatitis A Infection

	Never	Rarely	Sometimes	Often	DF	χ^2	p-value
No. 4							
LC non-cases	19	55	51	32	3	8.7	0.034*
LC cases	0	19	23	16			
PC non-cases	62	94	94	44			
PC cases	6	18	20	13			
No. 5							
LC non-cases	48	36	27	44	3	16.17	0.001*
LC cases	4	12	10	29			
PC non-cases	98	75	67	48			
PC cases	5	13	18	21			
No. 11							
LC non-cases	36	44	54	25	3	21.94	0.000*
LC cases	3	11	16	24			
PC non-cases	81	104	74	39			
PC cases	6	14	25	16			
No 14							
LC non-cases	70	35	40	11	3	7.94	0.047*
LC cases	16	22	11	5			
PC non-cases	120	84	62	24			
PC cases	21	16	14	6			
No. 15							
LC non-cases	94	34	17	12	3	10.72	0.013*
LC cases	22	13	15	6			
PC non-cases	173	82	28	7			
PC cases	20	23	8	5			
No. 17							
LC non-cases	77	62	10	8	3	9.46	0.024*
LC cases	20	19	11	3			
PC non-cases	170	91	25	4			
PC cases	21	16	16	5			
No. 18							
LC non-cases	78	52	19	12	3	9.17	0.027*
LC cases	17	16	13	8			
PC non-cases	170	83	29	9			
PC cases	18	17	14	8			

Table 5. (Continued)

	Never	Rarely	Sometimes	Often	DF	χ^2	p-value
No. 21							
LC non-cases	124	28	4	0	3	11.2	0.011*
LC cases	31	14	5	1			
PC non-cases	228	52	8	2			
PC cases	42	12	1	0			
No. 22							
LC non-cases	108	24	17	6	3	14.15	0.003*
LC cases	23	18	9	5			
PC non-cases	208	52	24	7			
PC cases	29	12	8	9			
No. 23							
LC non-cases	76	30	28	28	3	22.61	0.000*
LC cases	8	15	15	22			
PC non-cases	199	60	23	10			
PC cases	16	22	19	15			
No. 24							
LC non-cases	84	30	29	17	3	32.87	0.000*
LC cases	6	18	16	17			
PC non-cases	198	63	25	4			
PC cases	20	14	18	9			
No. 25							
LC non-cases	100	48	7	0	3	9.44	0.024*
LC cases	34	13	3	3			
PC non-cases	177	89	14	4			
PC cases	38	18	2	0			
No. 28							
LC non-cases	59	28	23	18	3	8.37	0.039*
LC cases	23	15	7	0			
PC non-cases	120	62	41	27			
PC cases	23	19	1	5			

* $p<0.05$

Table 6. χ^2-for-Trend Analysis of Exposure to Public Eating Places and Hepatitis A Infection

	Never	Rarely	Sometimes	Often	DF	χ^2	p-value
No. 4 (OR)							
Laboratory	1	?	?	?	1	5.75	0.016*
Classification	1	1.98	2.20	3.05			
No. 5 (OR)							
Laboratory	1	0.00	4.44	7.91	1	15.16	0.000*
Classification	1	3.40	5.27	8.58			
No. 11 (OR)							
Laboratory	1	3	3.56	11.5	1	18.56	0.000*
Classification	1	1.82	4.56	5.54			
No. 13 (OR)							
Laboratory	1	2.06	2.97	0	1	6.7	0.010*
Classification	1	1.66	0.71	2.46			
No. 15 (OR)							
Laboratory	1	1.63	3.77	2.14	1	7.62	0.006*
Classification	1	2.43	2.47	6.18			
No. 17 (OR)							
Laboratory	1	1.18	4.24	1.44	1	4.02	0.045*
Classification	1	1.42	5.18	10.1			
No. 18 (OR)							
Laboratory	1	1.41	3.14	3.06	1	8.18	0.004*
Classification	1	1.93	4.56	8.40			
No 21 (OR)							
Laboratory	1	2	5	?	1	10.41	0.001*
Classification	1	1.25	0.68	0			

Table 6. (Continued)

	Never	Rarely	Sometimes	Often	DF	χ^2	p-value
No. 22 (OR)							
Laboratory	1	3.52	2.49	3.91	1	9.63	0.002*
Classification	1	1.66	2.39	9.22			
No. 23 (OR)							
Laboratory	1	4.75	5.09	7 46	1	19.92	0.000*
Classification	1	2.49	10.3	10 7			
No. 24 (OR)							
Laboratory	1	8.4	7.72	14	1	27.57	0.000*
Classification	1	2.2	7.13	22.3			
No. 26 (OR)							
Laboratory	1	0.72	0.61	0.26	1	5 06	0.024*
Classification	1	1.78	0.68	0.25			
No. 28 (OR)							
Laboratory	1	1.37	0.78	0	1	3.97	0.046*
Classification	1	1.60	0.13	0.97			

* $p<0.05$
?: ∞ (infinite)

Table 7. Multivariate Analysis of Public Eating Places and Hepatitis A Infection

	Coefficient	SE	χ^2_1	p-value
Intercept	−5.3741	0.6249	73.9573	0.0001
No. 5	0.4415	0 1614	7.4772	0 0062*
No. 11	0.3823	0.1745	4.8007	0 0284*
No. 23	0.7323	0.1512	23.4667	0 0001*

* $p<0.05$

(3) Analysis of multiple risk factors

When drinking water, public eating places and places of resident were put into a model for analysis, it was found that only the places of residence. Nos. 5 and 23 eating places were positively related (Table 8).

Table 8. Multivariate Analysis of Risk Factors and Hepatitis A Infection

	Coefficient	SE	χ^2	p-value
Intercept	−4.0741	1.2835	10.0754	0.0015
Use of underground water	0.2595	0.5038	0.2653	0.6065
Use of tap water	0.0089	0.5021	0.0003	0.9859
Use of mineral water	0.7883	0.6003	1.7242	0.1892
Place of residence	1.1307	0.4513	6.2780	0.0122*
No. 5 eating place	0.4890	0.2152	5.1617	0.0231*
No. 23 eating place	0.5060	0.2565	3.8937	0.0485*

* $p<0.05$

3. Laboratory Testings of Human Specimens:

Of the 1,729 specimens collected from students, 176 were found anti-HAV (+) but IgM anti-HAV(−). The hepatitis A antibody positive rate of the students was 10.2%. Again, of all specimens, 126 were found IgM anti-HAV (+), giving an attack rate of 8.1%, and a susceptible rate of 89.8%. No hepatitis A infection, that is, IgM anti-HAV(−), was found in specimens collected from teachers and other staff members of the college.

Of the 47 cooks and workers, no hepatitis A infection, that is, 1gM anti-HAV (−). was found.

Testings of hepatitis A antibody for the 51 community residents found that four of them were IgM anti-HAV (+): and 35 of them, anti-HAV (+), giving an attack rate of 25% (4/51-35).

4. Laboratory Testings of Environmental Specimens.

From the underground water specimens collected from the off-campus rooms of students, an exceedingly large amount of coliform (coliform 6 MPN/ml) and E. coli was found; and the chloride residue in the tap water was 0. Students mentioned that tap water pipes were installed only at the beginning of the year (1995) just before the beginning of school. Tap water was available only from the drinking fountains, and underground water was used for washing. The investigation also revealed that the distance between the septic tanks and the underground water in the community was very close, only around 3 meters. Human wastes in the toilet soon discharged through the ditches along the two sides of the houses all over and into the ground underneath.

5. Laboratory Testings of Underground Water:

Only underground water specimens from an apartment where more cased were found showed red color. Nothing particular was detected from other areas. This showed a clustering of cases in that particular apartment.

5. Discussion

The history of hepatitis A virus could be traced back to the large-scale epidemic of jaundice in the army in the Middle Age. Even as recent as the Korean War and the Vietnam War, large-scale epidemics also occurred. The virus, however, was first planted on experimental animals only in 1970's, and was isolated the first time from cell culture in 1979. Hepatitis A virus is a small, single-strained RNA rims. One will not become chronic carrier of virus after infection, and immunity is 1ife-long¡¦. The mode of transmission is often through the fecal-oral route, by, for instance, contaminated food, drinking water or hands. Sporadic infections often occur in people living with patients by person-to-person contact, or large-scale outbreak through contaminated food or source of drinking water. The incubation period is 2-6 weeks after infection (average 25 days). Usually, before an outbreak, sporadic cases often occur 1-2 months before. This is because patients can discharge a large amount of virus in the feces 1-2 weeks before the onset of symptoms. Symptoms of hepatitis A though vary with age, the major symptoms are: nausea/vomiting, jaundice, diarrhea, brown urine, grey feces, tiredness, fever, anorexia, muscle pain and others. Many cases are mild, especially in children under two years. Acute hepatitis may occur in the elderly people. Fatality is generally around 0.6% [1-3] though higher in the elderly patients with acute hepatitis.

Hepatitis A infection is often through drinking water and other common sources of infection contaminated by feces. In the United States, the major risk factors of hepatitis A infection are: contact with patient (26%), homosexuality (15%), international traveling (14%), and infection from nurseries to homes (11%). For the rest 40%, no definite routes of transmission can be traced. Seroepidemiologic studies also show that hepatitis A infection is highly related to age and social-economic status, though not to sex and ethnic groups. Around 20% of Americans will have been infected and developed immunity by the age 20: this figure goes up to 50% by the age 50[4-6]. In Taiwan, studies of the prevalence of hepatitis A antibody in junior high school students show that the prevalence had dropped from 91.5% in 1970's [7] to 10.1% in 1991[8]. Wang et al. in their 1993 screening for hepatitis A antibody in all junior high school students around the Island found that the antibody prevalence of metropolitan area students was 13.3%; that of the urban area students, 17.7%; rural area students, 31.7%; and mountain area students, 94.5%(8). Beasley and Hwang in their 1983 follow-up screening of hepatitis A in students of a university found that 31.0% of them were susceptible. After four years of follow-up, 1 .7% had been infected. The annual incidence of hepatitis A was thus estimated to be 0.5% [9] Chen et al. in their 1983 study of a hepatitis A outbreak in a university in Taoyuan gave an attack rate of 30.4% and a susceptible rate of 24.4%. Of all infections, only 13% were asymptomatic. The symptoms were typical of hepatitis A infection [10].

It was found in the present investigation that the incident was associated with the community around the college. This finding corresponded to the assumption that community was the common source of the hepatitis A infection. Since the community was considered the source of infection, its common source of infection, such as drinking water, exposure to the public eating places, and places of residence, was investigated. The findings were that, in the single variate analysis, the drinking water and several public eating places were positively associated with the hepatitis A infection; and that, in the multivariate analysis when different kinds of drinking water were controlled, the relationship of drinking water to infection was not significant,; and when the mutual interference of different eating places was controlled, only Nos. 5, 11 and 23 eating places were significantly related. When places of residence, drinking water and exposure to eating places were controlled at the same time, the relationship of the exposure to drinking water was explained away by the eating places, and only places of residence and Nos. 5 and 23 eating places were found significantly related. Therefore, it was estimated that the present hepatitis A outbreak was significantly associated with Nos. 5 and 23 eating places. It was also noted from the χ^2-trend testing that exposure to Nos. 5 and 23 eating places and the hepatitis A infection had a significant dose-response effect.

In the multi-factor model of epidemiology, the drinking water, exposure to public eating places and person-to-person contact are the sufficient factors, and their common necessary factor is the hepatitis A virus. To cause hepatitis A infection, there must be one of the three sufficient factors. However, without the necessary factor, the mere existence of the three sufficient factors alone can not induce infection. Therefore, the necessary factor is an important factor that decides whether infection will take place. From the present investigation, it was found that not all hepatitis A cases were exposed to any one of the sufficient factors. Though exposure to public eating places was statistically significant, that is, the exposure to public eating places was the cause of this hepatitis A outbreak, it could be that those who ate at these public eating places had washed with underground water that had been contaminated by feces containing hepatitis A virus; it could have also been due to poor cooking. Those infected persons who did not eat at these public eating places could have drunk underground water already contaminated by feces of hepatitis A patients; they could have had close contacts with patients. The attributable proportion (AP) of each sufficient factor to hepatitis A could then be calculated. That is, of all cases, how many were caused by a particular sufficient factor: and, if this particular factor was removed, how many cases could have been averted. From the multivariate analysis, the AP for exposure to drinking water was 22.8%; that for exposure to No. 5 eating place was 38.7%; and that for exposure to No. 23 eating place was 39.7%. If the samples selected for the study could represent the entire population, that is, the exposure data of the samples were randomly distributed, and the incidence of the samples was that of the population, then the attributable risk of the population (ARp) could be calculated at the same time. The ARp of exposure to drinking water was 5.6%; that of exposure to No. 5 eating place was 11.8%; and that of exposure to No. 23 eating place was 12.2%.

6. Recommendations

1. The environmental sanitation of the area, particularly the quality of drinking water, should be improved. The use of underground water should be prohibited. The distance between the septic tank and the well or water pipe should be more than three meters to avoid any contamination.

2. The sanitary conditions of the public eating places around the college should be strictly supervised according to the Law of Food Sanitation.

3. Young students often are low in hepatitis A antibody, and therefore, an outbreak will often cause many infections. The inoculation of hepatitis A vaccines to students should be considered.

4. A disease surveillance system in school should be established. An outbreak can thus be reported immediately to better grasp the disease situations.

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