Evaluation of factors affecting variations in influenza A/H1N1 history in university students, Japan

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Abstract

Although the natural history of H1N1 has been found to vary among patients, little is known about the factors that affect these variations. Infected patients with an extended infection history may shed virus longer and spread infection. To further clarify these variations, we evaluated the natural history of H1N1 infection in 324 university students using a descriptive epidemiological method and analyzed factors affecting the natural history of infection. The median times from infection to fever development and from fever development to cure were 2 days (range 0-8 days) and 5 days (range 1-12 days), respectively, and the median time not attending classes was 5 days (range, 1-13 days). Variations in H1N1 natural history were associated with both environmental and individual factors, including route of infection, grade, gender, epidemic period, respiratory and gastrointestinal symptoms and headache. Steps affecting these factors may help control variations in H1N1 natural history and may enhance infection control measures.

Keyword: Influenza A/H1N1, University students, Natural history, Epidemiology

Introduction

During the worldwide outbreak of swine-origin influenza A/H1N1 virus in 2009 [1], several outbreaks occurred in schools [2-5]. The spread of infection in schools was due to close social networks of students rather via mixing with individuals of other generations [6]. Students gathered in class and in organized activities [3], whereas younger individuals may have lacked the cross-reactive protection seen in older people [7]. Therefore, primary infection control measures in schools are important in preventing community-wide H1N1 epidemics [8].

Infection control measures have included vaccination [9], with school closings recommended by educational organizations [10]. Although the actual effectiveness of these measures has been determined [11-13], basic epidemiological information on H1N1 remains insufficient. For example, H1N1 natural history varies among individuals, including variations in incubation period [14], time to recovery [2] and absence from school [15]. To date, however, little is known about the factors that affect these variations, suggesting that these factors may become confounders in evaluating the effects of vaccination or school closure. In addition, the spread of H1N1 influenza was greater than that of seasonal influenza, such that patients with an extended history of H1N1 infection may infect others. Identification of factors affecting the extension of natural history may help in controlling infection of high risk patients.

To identify the factors associated with inter-individual variations in H1N1 natural history, we

analyzed the natural history of individuals infected during the 2009 pandemic using a descriptive epidemiological method, and we assessed the associations between environmental and individual factors and variations in the natural history of infection.

Materials and Methods

Study population

This study was performed at Shinshu University, a local university in Japan [4] with approximately 12,000 students belonging to eight faculties (Arts, Agriculture, Economics, Education, Engineering, Medicine, Science, and Textile Science and Technology) at six campuses, all located in Nagano prefecture. About 10% of all students, especially freshmen, live in student housing, with most others living in apartments. All students were monitored during the H1N1 pandemic season from September 2009 to March 2010, and all students diagnosed with H1N1 during this time period were included in this study. The study design was reviewed and approved by the Committee for Medical Ethics of Shinshu University (approval number 1616), which waived the requirement for written informed consent because this study was based only on anonymous statistical data and did not involve any disadvantages to students.

Circumstance of H1N1 infection and precaution measure taken

The circumstances of and precaution measures for H1N1 infection have been described [4]. Briefly, H1N1 first broke out at Shinshu University in September 2009. Measures taken to prevent spread, including handwashing, gargling and wearing masks, were publicized in circulars and web pages at the University. Although vaccination was recommended, the amount of vaccine in the district was

insufficient and available to few students throughout the epidemic. Students who developed fever were required to visit a hospital or clinic, and those diagnosed with confirmed, probable or suspected H1N1 were instructed to telephone a designated person at the University. H1N1 diagnosis was based on the results of a rapid diagnosis kit and clinical symptoms, in accordance with the diagnostic criteria for H1N1 [16] at that time. The patients diagnosed with H1N1 infection may have included individuals infected with seasonal influenza or any other flu-like viruses, resulting in an overestimation of the number of individuals infected with H1N1. However, because almost all patients diagnosed with influenza during this time period were infected with H1N1 [17], we regarded all of these patients as positive for H1N1 in this study. The designated person at the university interviewed and recorded the characteristics of each student, including name, gender, age, grade and faculty, as well as information on H1N1 infection, including the dates of fever onset and hospital visit, symptoms, the date and route of infection and body temperature. While club activity at the university was suspended several times [18], the school was not closed to university students during this period.

H1N1 natural history

Self-reported information on all students was recorded, including date of infection, date of close contact with an H1N1-infected patient or exposure to a group or individual suspected of being

infected with H1N1; date of fever development; date of consultation, defined as visiting a hospital or clinic; and date of contact with the designated person at the university. The latter told all patients to stop attending classes and directed them to stay home for 2 days after body temperature returned to normal [19]. Students were also required to report the date they returned to classes, which was defined as the cure date in this study, with the period between starting absence and cure date defined as the period attendance was suspended. Because we investigated subjects by interviews and could not obtain laboratory data, data obtained from subjects may not correspond with their actual natural history of H1N1 infection. This interview method, used in previous studies [2, 20], has been reported to be reliable. We therefore regarded these data in our study as acceptable. In addition, all data were represented as calendar days because hourly data were not reported. Figure 1 illustrates the method of determining time intervals.

Statistical analysis

All times were expressed as medians and ranges, along with 95% upper limits. To evaluate factors affecting variations in natural history, some environmental and individual factors were analyzed for their association with natural history. Independent variables included university grade (1, 2, 3, 4 or over), gender (male, female), epidemic period (primary, from September to October 2009; secondary, from November 2009 to March 2010), infection route (inside/outside the university), fever (< or

≥37.8°C), treatment with anti-viral drug (oseltamivir or zanamivir; yes/no), respiratory symptoms (yes/no), gastrointestinal symptoms (yes/no), musculoskeletal symptoms (yes/no), headache (yes/no) and chills (yes/no). Because the activity of subjects in this study was characterized by grade and there was a correlation between age and grade, age was integrated into grade for analysis. Times of H1N1 natural history were dichotomized based on medians and categorized into normal and extended groups, with both considered dependent variables. Odds ratios (OR) of independent variables were estimated using univariate and multivariate logistic regression analyses. The multivariate model was adjusted for other independent variables. $P<0.05$ was considered statistically significant. PASW 18 software (SPSS Inc., Chicago, IL, USA) was used for all analyses.

Results

Descriptive epidemiology

Of the approximately 12,000 students enrolled at Shinshu University, 1016 called the designated person to report definite, probable, or possible H1N1 infection. Subjects with incomplete information were excluded, including seven for gender or grade, 63 for onset date, 11 for date of consultation, 12 for cure date, 135 for body temperature and 464 for route or date of infection. Thus, of the 1016 subjects, 324 (31.9%) were analyzed in this study. Table 1 shows the natural history of H1N1 infection in these subjects. All times were distributed non-parametrically. The median time from infection to fever development was 2 days (range 0-8 days), and the median time from fever to cure was 5 days (range, 1-12 days). The median time from fever development to consultation at a hospital or clinic was 1 day (range, 0-5 days), the median time from consultation to reporting to the designated person at the university was 0 days (range, 0-18 days), and the median time of suspension of attendance was 5 days (range, 1-13 days). A few students had a minimum cure time or a suspension of attendance of <2 days, since they resumed going to school before their body temperatures returned to normal. In addition, some students telephoned the designated university well after consultation, such that their report times were longer than their cure times.

We excluded 464 of the 1016 students (45.7%) from complete analysis because their infection information was incomplete. We could only assess their natural history after developing a fever

(Appendix 1); a comparison of these subjects with the 324 fully analyzed individuals showed no significant differences.

Factors affecting the natural history of H1N1 infection

To assess factors affecting time variations in the natural history of H1N1 infection, we dichotomized time variations and analyzed the odds ratios of factors affecting these variations (Appendices 2-5). Correlation matrices made among independent variables confirmed that all correlations were below 0.3, with no multicollinearity. Anti-viral medication was analyzed only after consultation. Multivariate analysis showed that the time between infection and consultation was significantly associated with infection outside the university (OR=1.87, 95% CI 1.03-3.41, $P<0.05$) and gastrointestinal symptoms (OR=0.40, 95% CI 0.18-0.90, $P<0.05$). The time from developing fever to reporting illness was significantly associated with being in the third year of university (OR=0.46, 95% CI 0.21-0.99, $P<0.05$), respiratory symptoms (OR=0.44, 95% CI 0.22-0.90, $P<0.05$) and headache (OR=0.60, 95% CI 0.37-0.98, $P<0.05$), and the time between consultation and reporting was significantly associated with female gender (OR=1.62, 95% CI 1.00-2.63, $P<0.05$). Secondary epidemic (OR=0.39, 95% CI 0.18-0.85, $P<0.05$) was the only factor significantly associated with the suspension of attendance (Table 2).

Discussion

We have assessed the natural history of H1N1 infection among university students using descriptive epidemiological methods, as well as analyzing the factors affecting various time intervals using a multivariate logistic regression model. Because this study was based on interviews or self-reports, our epidemiological evidence may be limited. Additional epidemiological studies of H1N1 are required, especially evidence of H1N1 epidemiology among schools attended by many individuals highly sensitive to infection. Moreover, fundamental data of H1N1 descriptive epidemiology should be accumulated to construct further infection control measures. Our results provide evidence of H1N1 epidemiology, showing that several environmental and individual factors affected variations in the natural history of H1N1 infection.

We found that the median time between infection and fever development was 2 days, with a range of 0-8 days. Previous reports showed similar results, with median incubation periods of 1.6 [14] and 1.6-1.7 [20] days, and ranges of 1-7 [21] and 2-7 [6] days. We also found that the median time between developing a fever and cure was 5 days, similar to the median 6 days previously reported [2]. Thus, the median time between infection and cure was 7 days, with a 95% upper limit of 12 days, indicating that half of these university students were cured of H1N1 infection at 1 week and almost all within 2 weeks. These results should be considered when deciding whether to institute infection control measures such as school closure. Moreover, the most important time interval associated with

control is the duration of virus shedding. Shedding of seasonal influenza virus peaks 2-3 days after infection [22] and continues for approximately 7 days [23]. In comparison, the shedding duration of H1N1 2009 was shown to be 5 days [2, 24], continuing for up to 13 days [25]. Although we did not assess the duration of virus shedding, the virus shedding period should also be considered when implementing infection control measures.

The median time between developing a fever and consultation was 1 day, with a 95% upper limit of 2 days, indicating that almost all subjects had visited a hospital or clinic within 2 days of fever development. Furthermore, the median time between consultation and reporting was 0 days, indicating that more than half the infected subjects immediately telephoned the university. Some students, however, reported to the university over 2 weeks later. Delays in notification have been reported for several infectious diseases, including measles, scarlet fever and meningitis [26], due to the rarity of the disease, difficulties in diagnosis or differences in administration. Delayed reporting of H1N1 infection was likely due to individual forgetfulness. Forgetting to make reports may result in loss of indication to the university and may trigger the spread of infection. Thus, prior to epidemics of novel infectious diseases, infection control information should be fully disseminated to all subjects, and all should be required to immediately report infection to a central location, thus preventing the spread of infection.

Subjects diagnosed with H1N1 infection were required to suspend school attendance, from at least

the time of consultation to 2 days after their body temperature returned to normal. Thus, the median duration of suspended attendance was 5 days and the 95% upper limit was 9 days. Although data on absences are usually used in surveillance systems [27, 28], data on the number of days absent tend to be ignored. However, this information is necessary to evaluate the characteristics of H1N1 and to implement further infection control measures such as school closure. Moreover, there is little epidemiological information on absence from school due to H1N1 infection [5]. The average duration of absence of Italian subjects infected with seasonal influenza was 5.1 days [29], similar to our findings. In the UK, however, the average duration of absence was 1.8 days [15]. This disparity may be due to differences in absence rules formulated by school organizations. In addition, these previous studies evaluated season influenza infection, whereas we evaluated H1N1 influenza.

We also evaluated environmental and individual factors affecting the natural history of H1N1 infection. All time intervals were dichotomized and factors affecting each time interval were analyzed using a multivariate model. We found that several environmental and individual factors were associated with time intervals. For example, we found that the time between developing a fever and reporting H1N1 infection was significantly shorter in third year than in other university students. Because most third year students at Shinshu University search for jobs, they might want the university to know about illnesses earlier to avoid problems. In addition, the time between consultation at a clinic or hospital and reporting infection was significantly longer for female than

for male students. This was not likely caused by differences in H1N1 prevalence, since the latter was not dependent on gender [4]. In general, females tend to be more anxious than males [30, 31]; therefore, female students may be more afraid of disadvantages (e.g. gossip or estrangement) caused by notifying the university and may report infections later than male students.

We also found that the time between infection and consultation was longer in individuals infected outside than inside the university. Interviews of H1N1 infected students infected far from the university, while either traveling or working at a job, confirmed that they did not carry a health insurance card or that they were strangers in the area of the infection. Therefore, they may not have visited a hospital or clinic immediately. In addition, the length of absence of H1N1 infected students was significantly shorter when they were infected during the secondary than during the primary epidemic period. Because the H1N1 subtype throughout the study period was identical [17, 32], virus subtype was unlikely to affect the condition of subjects. This difference may therefore have been due to differences in individual knowledge or in respondents [33]. Students realized that H1N1 pathogenicity was not severe during the middle of this pandemic, and students infected during the secondary epidemic period were less likely to report information on H1N1 to the university and to return to class earlier. Hence, student activity may change as information on the toxicity of a novel strain of influenza becomes more available.

The time between infection and consultation was shorter in students with than without

gastrointestinal symptoms, and the time between developing a fever and reporting was shorter in students with than without respiratory symptoms or headache. These results suggest that students with gastrointestinal symptoms may be concerned by their inability to eat and may therefore visit the hospital earlier. In addition, students with respiratory symptoms or headache may realize that they are infected with H1N1 and may notify the university earlier. Although university students with an influenza like illness reported several symptoms [34], there was no association between symptoms and H1N1 natural history. In addition to observing associations between symptoms and H1N1 natural history, we expected that specific symptoms would be associated with time to cure, because H1N1 infected patients with underlying diseases may develop a more severe illness [35, 36]. However, we did not observe any association between symptoms and time to cure, a finding that may be due to the self-reporting of symptoms.

Analysis of our data (Appendices 2-5) showed no other associations than those expected before the study. For example, anti-viral medication did not affect the time intervals of H1N1 infection. Because the effects of anti-viral medications are reduced if given a long time after infection [37], some students who consulted a doctor later were not medicated. Thus, medication may not be associated with time to cure or time absent from class. In addition, because fever was a necessary criterion for influenza-like illness [9], we expected that high body temperature would be associated with the time intervals of H1N1 natural history. However, no such association was observed. Since

body temperature was not associated with the degree of seriousness of infection [38], it may not be associated with the natural history of H1N1 infection. Moreover, subjects measured their own body temperatures, thus confounding our data. Overall, we found that the time intervals of H1N1 natural history were affected by the university environment and students' individual factors. These factors may become confounders when evaluating the effectiveness of preventive measures. Therefore, information on those factors may be helpful in controlling variations in the natural history of infection. In addition, supporting or changing these factors may improve the natural history of infection and may contribute to the improvement of additional infection control measures.

This study had several limitations. First, selection bias may have occurred, because this study was performed at only one university, with a study sample of approximately 1000 individuals. Moreover, complete information was only obtained from one third of these subjects, with data missing from the remainder. Almost all missing data were those associated with route or day of infection. A comparison of post-infection data from 464 students with incomplete information with data from the 324 subjects with complete information showed no significant differences between these two groups. Thus, our results are likely applicable to all infected individuals in this university. Additional studies involving other organizations and additional subjects may be necessary to exclude these selection biases and to obtain accurate data. Second, all data were based on self-reporting by university students, with some being erroneous. Therefore, data on infection date and infection route may not

be accurate. This limitation is generally encountered when using interviews to investigate infectious diseases. Previous reports using this interview method have yielded reliable results [2, 20], suggesting that our data were also reliable. Further study is needed to determine the precise reliability of the interview method. Third, we could only estimate factors contributing to longer or shorter time intervals of H1N1 history and could not determine the actual number of days. Development of an actual time estimation model requires additional samples and more precise information, including longitudinal data.

We have shown here that time intervals of H1N1 infection vary in university students and that extended time intervals were due to several environmental and individual factors. Information about these factors may be helpful in controlling variations in the natural history of H1N1 infection. Supporting or changing these factors may improve infection control measures. Additional longitudinal studies are necessary to clarify factors affecting the natural history of influenza H1N1 infection.

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Conflict of interest

None

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Figure legend

Figure 1. History of H1N1 influenza among students at Shinshu University.

Shown are the time intervals for H1N1 infection. For example, No. 1 indicates the time from infection to fever development. Each time interval is expressed as median, range and 95% limit in days.

Table 1. Natural history of H1N1 infected students (n=324)

No	H1N1 times	median	95%	range
1	Infection-fever development	2	4	0-8
2	Infection-consultation	3	6	0-9
3	Infection-report	3	6	0-22
4	Infection-cure	7	12	2-17
5	Fever development-consultation	1	2	0-5
6	Fever development-report	1	4	0-19
7	Fever development-cure	5	9	1-12
8	Consultation-report	0	3	0-18
9	Consultation-cure	4	8	1-12
10	Suspension of attendance	5	9	1-13

All data are expressed as days

Table2. Affecting factors for extension of H1N1 history

			2 infection-consultation				6 fever development-report				8 consultation-report				10 suspension of attendance			
			univariate		multivariate		univariate		multivariate		univariate		multivariate		univariate		multivariate	
Factor		n	OR	95%CI	OR	95%CI	OR	95%CI	OR	95%CI	OR	95%CI	OR	95%CI	OR	95%CI	OR	95%CI
Grade	1	138	1		1		1		1		1		1		1		1	
	2	97	1.44	0.85-2.44	1.39	0.79-2.42	1.03	0.61-1.76	1.06	0.60-1.87	0.77	0.45-1.31	0.68	0.38-1.20	1.28	0.76-2.18	1.40	0.79-2.46
	3	53	1.48	0.78-2.82	1.49	0.75-2.95	0.47*	0.23-0.97	0.46*	0.21-0.99	0.61	0.31-1.21	0.54	0.26-1.10	0.52*	0.27-0.99	0.56	0.28-1.11
	4 or over	36	1.36	0.65-2.86	1.17	0.53-2.55	1.43	0.69-3.00	1.66	0.75-3.66	1.27	0.61-2.66	1.26	0.58-2.75	1.24	0.59-2.63	1.44	0.66-3.18
Gender	Male	208	1		1		1		1		1		1		1		1	
	Female	116	1.07	0.68-1.69	1.02	0.63-1.64	1.33	0.84-2.13	1.48	0.90-2.42	1.53	0.96-2.44	1.62*	1.00-2.63	0.92	0.59-1.46	0.98	0.60-1.58
Epidemic period	Primary	38	1		1		1		1		1		1		1		1	
	Secondary	286	1.66	0.84-3.28	1.49	0.73-3.01	1.31	0.64-2.71	1.22	0.57-2.61	0.94	0.47-1.89	0.89	0.43-1.83	0.41*	0.19-0.86	0.39*	0.18-0.85
Infection route	Inside of university	256	1		1		1		1		1		1		1		1	
	Outside of university	68	2.04*	1.15-3.60	1.87*	1.03-3.41	1.07	0.61-1.85	0.99	0.54-1.80	1.08	0.62-1.87	1.11	0.62-2.00	0.70	0.41-1.20	0.66	0.37-1.19
Fever	~ 37.8 degree	77	1		1		1		1		1		1		1		1	
	37.8 degree or over	247	0.70	0.42-1.19	0.72	0.42-1.24	0.84	0.49-1.41	0.78	0.45-1.35	1.5	0.87-2.59	1.46	0.83-2.57	1.59	0.95-2.66	1.52	0.89-2.60
Anti-viral drug medication	No	43					1		1		1		1		1		1	
	Yes	281					0.57	0.30-1.09	0.53	0.27-1.05	0.94	0.49-1.81	0.91	0.46-1.80	1.10	0.58-2.10	0.97	0.50-1.90
Respiratory symptom	No	39	1		1		1		1		1		1		1		1	

	Yes	285	0.98	0.50-1.91	0.95	0.47-1.93	0.51	0.26-1.01	0.44*	0.22-0.90	0.61	0.31-1.20	0.57	0.29-1.15	1.37	0.70-2.67	1.33	0.66-2.70
Gastrointestinal symptom	No	294	1		1		1		1		1		1		1		1	
	Yes	30	0.42*	0.19-0.92	0.40*	0.18-0.90	0.84	0.38-1.85	1.00	0.43-2.32	1.46	0.69-3.11	1.57	0.72-3.45	1.22	0.57-2.63	1.30	0.57-2.94
Musculoskeletal symptom	No	225	1		1		1		1		1		1		1		1	
	Yes	99	0.98	0.61-1.58	0.94	0.56-1.56	0.85	0.52-1.39	0.88	0.51-1.49	1.21	0.75-1.96	1.16	0.69-1.94	1.13	0.70-1.81	1.18	0.70-1.97
Headache	No	177	1		1		1		1		1		1		1		1	
	Yes	147	0.99	0.64-1.54	0.98	0.61-1.56	0.60*	0.38-0.95	0.60*	0.37-0.98	0.89	0.57-1.39	0.87	0.54-1.41	0.92	0.59-1.43	0.94	0.58-1.50
Chills	No	298	1		1		1		1		1		1		1		1	
	Yes	26	1.08	0.48-2.44	1.00	0.43-2.31	1.07	0.47-2.44	1.08	0.46-2.56	0.84	0.36-1.95	0.90	0.37-2.16	2.31	0.94-5.66	2.36	0.94-5.98

Variables are adjusted for each other in the multivariate model, * P<0.05

Appendix 1. Natural history of H1N1 infected students (n=464)

No	H1N1 times	median	95%	range
5	Fever development-consultation	1	2	0-7
6	Fever development-report	2	7	0-28
7	Fever development-cure	5	9	0-21
8	Consultation-report	0	6	0-27
9	Consultation-cure	4	8	0-20
10	Suspension of attendance	5	9	1-20

All data are expressed as days

Appendix 2. Factors affecting time intervals of H1N1 natural history from time of infection

			1 Infection-fever development				2 Infection-consultation				3 Infection-report				4 Infection-cure			
			univariate		multivariate		univariate		multivariate		univariate		multivariate		univariate		multivariate	
Factor		n	OR	95%CI	OR	95%CI	OR	95%CI	OR	95%CI	OR	95%CI	OR	95%CI	OR	95%CI	OR	95%CI
Grade	1	138	1		1		1		1		1		1		1		1	
	2	97	1.35	0.78-2.32	1.26	0.71-2.22	1.44	0.85-2.44	1.39	0.79-2.42	1.13	0.63-2.04	1.08	0.58-2.01	1.09	0.64-1.83	1.03	0.59-1.78
	3	53	1.68	0.84-3.34	1.60	0.78-3.28	1.48	0.78-2.82	1.49	0.75-2.95	1.10	0.54-2.24	1.07	0.50-2.28	0.57	0.30-1.08	0.56	0.29-1.11
	4 or over	36	1.51	0.69-3.31	1.31	0.58-2.96	1.36	0.65-2.86	1.17	0.53-2.55	1.63	0.66-4.03	1.55	0.60-4.01	1.73	0.80-3.73	1.68	0.75-3.76
Gender	Male	208	1		1		1		1		1		1		1		1	
	Female	116	1.16	0.72-1.87	1.12	0.68-1.84	1.07	0.68-1.69	1.02	0.63-1.64	1.37	0.81-2.33	1.36	0.78-2.36	1.18	0.75-1.86	1.20	0.74-1.94
Epidemic period	Primary	38	1		1		1		1		1		1		1		1	
	Secondary	286	1.60	0.81-3.18	1.48	0.73-3.00	1.66	0.84-3.28	1.49	0.73-3.01	1.55	0.75-3.18	1.43	0.67-3.06	1.04	0.53-2.04	0.95	0.47-1.93
Infection route	Inside of university	256	1		1		1		1		1		1		1		1	
	Outside of university	68	1.64	0.90-2.97	1.46	0.78-2.73	2.04*	1.15-3.60	1.87*	1.03-3.41	1.86	0.94-3.67	1.72	0.84-3.52	1.32	0.77-2.27	1.23	0.69-2.20
Fever	~ 37.8 degree	77	1		1		1		1		1		1		1		1	
	37.8 degree or over	247	0.74	0.43-1.29	0.74	0.42-1.30	0.70	0.42-1.19	0.72	0.42-1.24	0.61	0.33-1.15	0.61	0.32-1.16	1.24	0.74-2.06	1.18	0.69-2.00
Anti-viral drug medication	No	43									1		1		1		1	
	Yes	281									0.83	0.39-1.77	0.90	0.41-1.97	0.80	0.42-1.53	0.77	0.39-1.51
Respiratory symptom	No	39	1		1		1		1		1		1		1		1	
	Yes	285	1.19	0.60-2.38	1.16	0.57-2.37	0.98	0.50-1.91	0.95	0.47-1.93	0.70	0.31-1.58	0.67	0.28-1.57	0.98	0.50-1.92	0.96	0.47-1.94
Gastrointestinal symptom	No	294	1		1		1		1		1		1		1		1	
	Yes	30	0.92	0.42-2.00	0.92	0.41-2.08	0.42*	0.19-0.92	0.40*	0.18-0.90	0.50	0.23-1.08	0.52	0.23-1.18	0.64	0.30-1.37	0.71	0.32-1.58

Musculoskeletal symptom	No	225	1		1		1		1		1		1		1		1	
	Yes	99	0.97	0.59-1.59	0.89	0.53-1.51	0.98	0.61-1.58	0.94	0.56-1.56	1.16	0.67-2.01	1.20	0.67-2.15	1.44	0.89-2.32	1.57	0.94-2.62
Headache	No	177	1		1		1		1		1		1		1		1	
	Yes	147	1.20	0.76-1.90	1.13	0.70-1.84	0.99	0.64-1.54	0.98	0.61-1.56	0.71	0.43-1.16	0.65	0.38-1.10	0.69	0.44-1.07	0.64	0.40-1.02
Chills	No	298	1		1		1		1		1		1		1		1	
	Yes	26	1.22	0.51-2.91	1.29	0.53-3.15	1.08	0.48-2.44	1.00	0.43-2.31	0.96	0.39-2.38	0.92	0.36-2.36	1.72	0.74-3.98	1.62	0.68-3.88

Variables were adjusted for each other in the multivariate model, * P<0.05

Appendix 3. Factors affecting time from fever development

			5 Fever development-consultation				6 Fever development-report				7 Fever development-cure			
			univariate		multivariate		univariate		multivariate		univariate		multivariate	
Factor		n	OR	95%CI	OR	95%CI	OR	95%CI	OR	95%CI	OR	95%CI	OR	95%CI
Grade	1	138	1		1		1		1		1		1	
	2	97	1.34	0.79-2.28	1.44	0.82-2.52	1.03	0.61-1.76	1.06	0.60-1.87	1.06	0.63-1.80	1.13	0.65-1.97
	3	53	1.05	0.55-1.97	1.15	0.59-2.25	0.47*	0.23-0.97	0.46*	0.21-0.99	0.49*	0.26-0.93	0.56	0.28-1.10
	4 or over	36	0.86	0.42-1.80	0.93	0.43-2.02	1.43	0.69-3.00	1.66	0.75-3.66	1.17	0.55-2.48	1.31	0.59-2.89
Gender	Male	208	1		1		1		1		1		1	
	Female	116	0.83	0.53-1.31	0.87	0.54-1.40	1.33	0.84-2.13	1.48	0.90-2.42	1.05	0.67-1.66	1.12	0.69-1.81
Epidemic period	Primary	38	1		1		1		1		1		1	
	Secondary	286	1.85	0.93-3.67	1.84	0.91-3.72	1.31	0.64-2.71	1.22	0.57-2.61	0.78	0.39-1.56	0.71	0.35-1.47
Infection route	Inside of university	256	1		1		1		1		1		1	
	Outside of university	68	1.18	0.69-2.04	1.07	0.60-1.91	1.07	0.61-1.85	0.99	0.54-1.80	0.89	0.52-1.52	0.85	0.48-1.52
Fever	~ 37.8 degree	77	1		1		1		1		1		1	
	37.8 degree or over	247	0.86	0.51-1.44	0.82	0.48-1.39	0.84	0.49-1.41	0.78	0.45-1.35	1.37	0.82-2.28	1.34	0.79-2.29
Anti-viral drug medication	No	43					1		1		1		1	
	Yes	281					0.57	0.30-1.09	0.53	0.27-1.05	0.70	0.36-1.35	0.62	0.31-1.23
Respiratory symptom	No	39	1		1		1		1		1		1	
	Yes	285	0.52	0.25-1.06	0.53	0.25-1.10	0.51	0.26-1.01	0.44*	0.22-0.90	1.20	0.61-2.34	1.16	0.57-2.34
Gastrointestinal symptom	No	294	1		1		1		1		1		1	
	Yes	30	0.67	0.32-1.43	0.69	0.31-1.50	0.84	0.38-1.85	1.00	0.43-2.32	0.59	0.28-1.26	0.66	0.30-1.45

Musculoskeletal symptom	No	225	1		1		1		1		1		1	
	Yes	99	0.84	0.52-1.35	0.89	0.54-1.48	0.85	0.52-1.39	0.88	0.51-1.49	1.02	0.63-1.64	1.13	0.68-1.88
Headache	No	177	1		1		1		1		1		1	
	Yes	147	0.71	0.46-1.11	0.75	0.47-1.20	0.60*	0.38-0.95	0.60*	0.37-0.98	0.66	0.42-1.03	0.67	0.42-1.07
Chills	No	298	1		1		1		1		1		1	
	Yes	26	1.56	0.68-3.62	1.41	0.59-3.36	1.07	0.47-2.44	1.08	0.46-2.56	2.34	0.96-5.74	2.20	0.87-5.55

Variables were adjusted for each other in the multivariate model, * P<0.05

Appendix 4. Factors affecting time from consultation

			8 Consultation-report				9 Consultation-cure			
			univariate		multivariate		univariate		multivariate	
Factor		n	OR	95%CI	OR	95%CI	OR	95%CI	OR	95%CI
Grade	1	138	1		1		1		1	
	2	97	0.77	0.45-1.31	0.68	0.38-1.20	0.96	0.56-1.65	1.05	0.59-1.86
	3	53	0.61	0.31-1.21	0.54	0.26-1.10	0.51*	0.27-0.96	0.53	0.27-1.05
	4 or over	36	1.27	0.61-2.66	1.26	0.58-2.75	1.14	0.52-2.47	1.28	0.57-2.89
Gender	Male	208	1		1		1		1	
	Female	116	1.53	0.96-2.44	1.62*	1.00-2.63	1.06	0.67-1.70	1.13	0.69-1.85
Epidemic period	Primary	38	1		1		1		1	
	Secondary	286	0.94	0.47-1.89	0.89	0.43-1.83	0.45*	0.20-0.98	0.45	0.20-1.02
Infection route	Inside of university	256	1		1		1		1	
	Outside of university	68	1.08	0.62-1.87	1.11	0.62-2.00	0.61	0.35-1.04	0.58	0.33-1.04
Fever	- 37.8 degree	77	1		1		1		1	
	37.8 degree or over	247	1.50	0.87-2.59	1.46	0.83-2.57	1.43	0.85-2.40	1.37	0.80-2.34
Anti-viral drug medication	No	43	1		1		1		1	
	Yes	281	0.94	0.49-1.81	0.91	0.46-1.80	1.03	0.54-1.99	0.92	0.47-1.81
Respiratory symptom	No	39	1		1		1		1	
	Yes	285	0.61	0.31-1.20	0.57	0.29-1.15	1.11	0.56-2.19	1.06	0.52-2.18
Gastrointestinal symptom	No	294	1		1		1		1	
	Yes	30	1.46	0.69-3.11	1.57	0.72-3.45	0.95	0.44-2.05	1.03	0.46-2.32
Musculoskeletal symptom	No	225	1		1		1		1	
	Yes	99	1.21	0.75-1.96	1.16	0.69-1.94	1.41	0.86-2.31	1.53	0.90-2.61
Headache	No	177	1		1		1		1	
	Yes	147	0.89	0.57-1.39	0.87	0.54-1.41	0.91	0.58-1.42	0.90	0.56-1.46
Chills	No	298	1		1		1		1	
	Yes	26	0.84	0.36-1.95	0.90	0.37-2.16	2.25	0.88-5.76	2.38	0.90-6.29

Variables were adjusted for each other in the multivariate model, * P<0.05

Appendix 5. Factors affecting number of days absent

			10 Suspension of attendance			
			univariate		multivariate	
Factor		n	OR	95%CI	OR	95%CI
Grade	1	138	1		1	
	2	97	1.28	0.76-2.18	1.40	0.79-2.46
	3	53	0.52*	0.27-0.99	0.56	0.28-1.11
	4 or over	36	1.24	0.59-2.63	1.44	0.66-3.18
Gender	Male	208	1		1	
	Female	116	0.92	0.59-1.46	0.98	0.60-1.58
Epidemic period	Primary	38	1		1	
	Secondary	286	0.41*	0.19-0.86	0.39*	0.18-0.85
Infection route	Inside of university	256	1		1	
	Outside of university	68	0.70	0.41-1.20	0.66	0.37-1.19
Fever	- 37.8 degree	77	1		1	
	37.8 degree or over	247	1.59	0.95-2.66	1.52	0.89-2.60
Anti-viral drug medication	No	43	1		1	
	Yes	281	1.10	0.58-2.10	0.97	0.50-1.90
Respiratory symptom	No	39	1		1	
	Yes	285	1.37	0.70-2.67	1.33	0.66-2.70
Gastrointestinal symptom	No	294	1		1	
	Yes	30	1.22	0.57-2.63	1.30	0.57-2.94
Musculoskeletal symptom	No	225	1		1	
	Yes	99	1.13	0.70-1.81	1.18	0.70-1.97
Headache	No	177	1		1	
	Yes	147	0.92	0.59-1.43	0.94	0.58-1.50
Chills	No	298	1		1	
	Yes	26	2.31	0.94-5.66	2.36	0.94-5.98

Variables were adjusted for each other in the multivariate model, * P<0.05