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Original Article

Epidemiological Investigation of the Outbreak of Acute Respiratory Infection caused by Adenovirus Type B55 in a Physical Education School in 2017

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Conflict of Interest
No conflicts of interest.

ABSTRACT

Background: On May 19, 2017, the cluster of 6 acute respiratory infections due to adenovirus in the swimming department of a physical education school (School J) was reported to Korea Centers for Disease Control and Prevention. An epidemiological investigation was conducted to identify the transmission route of the infection and to control the outbreak.
Materials and Methods: A retrospective cohort study (Study 1) was conducted on students and teachers of the athletic departments using the swimming pool, and a prospective surveillance (Study 2) was conducted on all students and teachers of the School J. A case was defined as any student and school personnel who developed more than two of the following symptoms from April 10 to July 2, 2017: fever, sore throat, cough, rhinorrhea, or headache. Relative risks (RRs) were calculated to compare the attack rates according to potential risk factors. Multivariable logistic regression was performed to identify the risk factors for infection in the outbreak.
Results: 47 cases were identified: 33 (55.9%) cases occurred among 59 students and teachers in Study 1 and 14 (3.9%) among 362 students and school personnel in Study 2. There were 18 laboratory confirmed adenovirus infection cases. The common symptoms were headache (71.7%), fever (69.6%), rhinorrhea (63.0%), sputum (56.5%), and sore throat (54.3%). 23.9% of the cases were accompanied with diarrhea and 19.6% with eye congestion. None of the cases developed pneumonia. 32.6% of the cases were hospitalized. In Study 1, attack rate in the swimming department was higher than that in others (RR: 1.90; 95% confidence interval [CI]: 1.01-3.60). In Study 2, being a member of the shooting department (RR: 20.70; 95% CI: 4.90 - 87.47) and being a first year high school student (RR: 10.95; 95% CI: 2.90 - 41.33) were identified as risk factors for the infections. Genetic analyses of the adenoviruses showed 100% identical sequence in homology and confirmed the human adenovirus B55 (HAdV-B55). No adenovirus was detected at examining the water and environment of the swimming pool and dormitory.
Conclusion: The outbreak is inferred to be occurred via propagated transmission among the students in the same athletic department, while the students with symptoms of respiratory infection continued performing school activities without any restrictions. Infection control measures such as early detection of symptoms of respiratory infection and restriction of group activity are necessary to prevent respiratory infection outbreak in the communal living setting.

Keywords: Human adenovirus; Outbreak; Acute respiratory infection; School

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Author Contributions

Conceptualization: JS, EC. Data curation: JS. Formal analysis: JS. Investigation: JS, HL, EC. Methodology: JS, EC. Supervision: EC. Validation: JS. Visualization: JS. Writing - original draft: JS. Writing - review & editing: JS, HL, EC.

INTRODUCTION

The adenovirus (HAdV) is a double-stranded DNA virus. It is divided into seven species by DNA homology and has more than 70 serotypes [1]. Depending on the serotype, HAdV causes various infectious diseases such as respiratory infections, gastroenteritis, and epidemic conjunctivitis. The most common infection due to HAdV is pharyngitis [2, 3]. Mainly developed among children, most of them recover naturally. However some cases progress to severe respiratory infection such as pneumonia and cause death. The known types that cause severe respiratory infection among adults are types 3, 4, and 7, and types 14 and 55 have been reported as the cause of outbreaks [4-9]. Adenovirus is transmitted via respiratory droplets, fecal to oral routes, or contaminated environments, and rarely via swimming pool water [10, 11]. The incubation period of an acute respiratory infection by adenovirus is 2~14 days [2]. Adenovirus infection outbreak in swimming pool, the healthcare facilities, and military camps have been reported [5, 12-15]. An oral vaccine has been introduced in the United States to prevent extensive epidemics of respiratory infections caused by types 4 and 7 in military camps [16]. In Korea, a severe case of adenovirus infection in a military camp, cases of pneumonia and consequent death caused by type 55 have been reported [17-20]. But there has been no report of adenovirus respiratory infection outbreak in schools, education facilities, and private residential facilities in Korea. This study is the first report of the outbreak of acute respiratory infection caused by adenovirus, occurred on school in Korea.

On May 19, 2017, the cluster of acute respiratory infections due to adenovirus in the swimming department of a physical education school (School J) was reported to Korea Centers for Disease Control and Prevention (KCDC). An epidemiological investigation was conducted to identify the transmission route of the infection and to control the outbreak. In this paper, we aim to recommend infection control measures for prevention of adenovirus respiratory infection outbreak through epidemiological analysis of the outbreak.

MATERIALS AND METHODS

The cluster of 6 respiratory infections was identified when the medical doctor who examined six students from the swimming department of School J with symptoms of acute respiratory infection reported to the public health center. Throat swabs were performed for symptomatic students in the swimming department, and adenovirus was detected from four students. Thus an epidemiological investigation was conducted suspecting the outbreak of acute respiratory infections by adenovirus to identify the transmission route of the infection and to control the outbreak.

1. Case definition and criteria for exception

A suspected case is defined as the person who has two or more of the following acute respiratory infection symptoms without laboratory confirmation: fever, sore throat, cough, rhinorrhea, and headache [2, 21]. A confirmed case is defined as the person who tested positive for adenovirus by the respiratory virus polymerase chain reaction (PCR), among the suspected cases. Cases from April 10 (14 days before the first identified case) to July 2 (14 days after the last identified case) are included, and cases who tested positive for virus other than adenovirus on PCR tests are excluded.

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2. Target population and study design

The physical education school J is an integrated school specialized in athletics education consisting of 12 classes, 2 classes per grade, with a total of 6 grades including middle and high school. The total school population was 395, consisting of 322 students and 73 teachers. Each student is a member of one of the16 athletic departments, and every student were accommodated in a campus dormitory. As all students with respiratory symptoms were identified as members of the departments using the swimming pool (swimming and modern sports) at the on-site investigation performed on May 22, a retrospective cohort investigation (Study 1) was conducted instantaneously on 59 students and teachers who had been using the swimming pool. And since 22 May prospective active surveillance (Study 2) has been conducted for all students and school personnel to detect additional cases. For the active surveillance, teachers of each class checked the students every morning for any symptoms of acute respiratory infection and reported the results to the public health center. Questionnaire survey and throat swab investigations were conducted on all 59 of swimming and modern sports departments and additional cases from active surveillance. Thirty three cases who were identified in Study 1 and 14 cases who were identified in Study 2 were enrolled as cases in the present study.

3. Data collection

Data on school activities of all students were collected from the list of names sorted out according to grades, classes, athletic departments, and dormitory rooms. Data such as sex, age, grades, classes, athletic departments, information on dormitory, onset of symptoms, history of medical treatments, information of using the swimming pool, and contacts with any person having respiratory symptom were collected by interviewing suspected cases.

4. Laboratory test

PCR tests were conducted on eight sentinel surveillance respiratory viruses including adenovirus by collecting the throat swab of target population for in Study 1 and suspected cases in Study 2. The eight respiratory viruses were as follows: adenovirus, human bocavirus, parainfluenza virus, respiratory syncytial virus, rhinovirus, human metapneumovirus, human coronavirus, and influenza virus. Adenovirus PCR tests were conducted by collecting the rectal swab, in addition to the throat swab, of a suspected case who had improved symptoms.

Specimen from the school environments were collected on May 20 and 22, and adenovirus PCR tests were conducted on 59 samples collected from the swimming pool water, surface of the swimming pool environment, and the surface of the dormitory environment. More than one liter of swimming pool water was collected and concentrated using concentration method (InnovaPrep® Concentrating Pipette) before PCR tests.

Viral sequencing analyses were performed on the detected adenoviruses using the HAdV hexon partial 904 base pairs.

5. Statistical analysis

To compare the attack rates based on the potential risk factors, the relative risks (RRs) were calculated and the statistical significance was evaluated by Fisher's exact test. Multivariable logistic regression was performed to identify the risk factors for infection in the outbreak. Statistical significance was identified with a 95% confidence interval and a *P*-value <0.05 in a two-tailed test. Epi-info™ (CDC, Atlanta, GA, USA) and SPSS (Version 25.0 for Windows: IBM, Armonk, NY, USA) were used for the statistical analysis.

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6. Ethics statement

The need for ethical approval for this study was waived, based on the *Korean Infectious Disease Control and Prevention Act. No. 4* and *Enforcement Rule of Bioethics and Safety Act.No.33.*

RESULTS

1. Extent of the outbreak and epidemic curve

In Study 1, a total of 33 cases were identified, of which 12 were confirmed cases and 21 were suspected cases and the attack rate was 55.9% (33/59). None of the asymptomatic cases tested positive for adenovirus. The first suspected case occurred on April 24. He was the first grade high school student (15 years old), was a member of the modern sports department, and had used the swimming pool continuously during the presence of symptoms. The second case occurred on April 25. He was a swimming teacher who was hospitalized due to the acute pharyngo-tonsillitis for 5 days (from April 25 to 29). At the time of specimen collection (May 22), the symptoms of the two cases had been disappeared. The first confirmed cases occurred on May 13. From May 13 to May 17, there was an increasing trend in the incidence of cases; on May 15, the most confirmed cases occurred (**Fig. 1**).

In Study 2, a total of 14 cases were identified, of which 6 were confirmed cases and 8 were suspected cases; the attack rate was 3.9% (14/362). Since the on-site investigation on May 22, sporadic cases occurred until June 18, which was the last case (**Fig. 1**). The outbreak period was 56 days.

2. Characteristics of the cases

There were 33 identified cases in Study 1, of which 32 were students and 1 was a swimming teacher. 23 (69.7%) of the 33 cases were male. 1st and 3rd grade of the high school had the largest number of the cases (8 each). Swimming and modern sports departments had 26 (78.8%) and 6 (18.2%) cases, respectively. There were 14 identified cases in Study 2, and all of them were students. Ten (71.4%) of these cases were male. Nine (64.3%) of the 14 cases were 1st grade students of the high school, and 6 (42.9%) were from the Shooting department. The common symptoms in 47 cases were headache (33, 71.7%), fever (32, 69.6%), rhinorrhea (29, 63.0%), sputum (26, 56.5%), and sore throat (25, 54.3%). Eleven (23.9%) cases were accompanied with vomiting or diarrhea, and 9 (19.6%) showed eye congestion. Although none of the cases showed signs of pneumonia, 15 (32.6%) of all cases were hospitalized due to acute respiratory infection (**Table 1**).

3. Comparison of attack rates

In Study 1, attack rate of the swimming department was higher than that of others (RR: 1.90; 95% confidence interval (CI): 1.01-3.60) (**Table 2**). In Study 2, being a member of the shooting department (RR: 20.70; 95% CI: 4.90 - 87.47) and being a first grade student of high school (RR: 10.95; 95% CI: 2.90 - 41.33) were identified as risk factors for infections, according to the results of multivariable logistic regression (**Table 3**).

4. Laboratory test

Adenovirus was detected in throat swabs in 11 out of 12 confirmed cases in Study 1, and the duration from symptom onset to specimen collection was 1 to 8 days (median 5 days). In one of 12 confirmed, adenovirus was not detected in the throat swab collected on day 9 after symptom onset, but detected in the rectal swab. Adenovirus was detected in throat swab in all 6 confirmed cases of Study 2, and the duration from symptom onset to specimen

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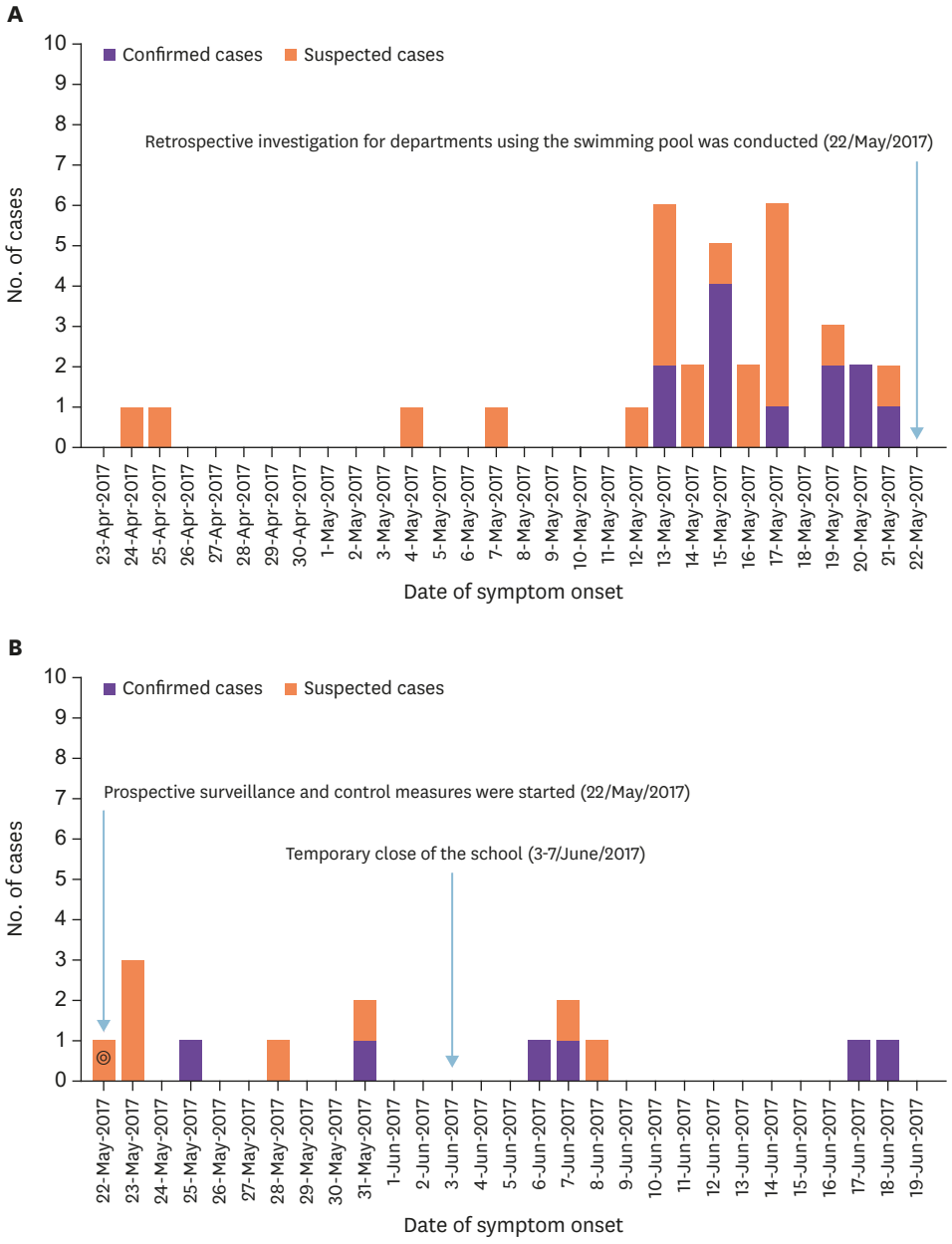

Figure 1. Epidemic curve of adenovirus respiratory infection in the retrospective investigation for departments using the swimming pool (Study 1), and in prospective surveillance for entire members in the physical education school (Study 2).
A. Retrospective investigation of members of departments using the swimming pool (Study 1).
B. Prospective surveillance of the entire members of the physical education school (Study 2).
The case marked "◎" was identified after the first field investigation on May 22. This case was enrolled in Study 2, not in Study 1.

collection was 1 to 7 days (median 1 day). Two of the confirmed cases were co-detected with influenza virus. No adenovirus but influenza virus was detected from a student among those with fever and respiratory symptoms. The student was not included in the cases.

As a result of the gene analysis on 14 specimen on which the sequence analysis was possible among 18 identified adenoviruses detected from the confirmed cases, the sequence was 100% identical in homology and the type was confirmed to be HAdV B-55.

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Table 1. Clinical characteristics of the adenovirus respiratory infection cases in the outbreak

Variables		Total (N = 47)		Confirmed cases (N = 18)		Suspected cases (N = 29)	
		N	%	N	%	N	%
Symptom	Headache	33	71.7	15	83.3	18	62.1
	Fever	32	69.6	15	83.3	17	58.6
	Rhinorrhea	29	63.0	7	38.9	22	75.9
	Sputum	26	56.5	7	38.9	19	65.5
	Sore throat	25	54.3	12	66.7	13	44.8
	Cough	20	43.5	3	16.7	17	58.6
	Chill	18	39.1	8	44.4	10	34.5
	Nausea	11	23.9	5	27.8	6	20.7
	Diarrhea	11	23.9	5	27.8	6	20.7
	Abdomen pain	9	19.6	6	33.3	3	10.3
	Eye congestion	9	19.6	5	27.8	4	13.8
	Dyspnea	8	17.4	6	33.3	2	6.9
	Myalgia	5	10.9	3	16.7	2	6.9
	Vomiting	4	8.7	1	5.6	3	10.3
	Dizziness	4	8.7	2	11.1	2	6.9
Co-detection with other respiratory viruses	Yes	2[a]	4.3	2	11.1	0	0.0
	No	45	95.7	16	88.9	29	100.0
Hospitalization	Yes	15	32.6	8	44.4	7	24.1
	No	32	69.6	10	55.6	22	75.9
Underlying disease	Yes	6[b]	12.8	1	5.6	5	17.2
	No	41	87.2	17	94.4	24	82.8
History of any medical surgery in the past	Yes	4[c]	8.5	0	0.0	4	13.8
	No	43	91.5	18	100.0	25	86.2

[a]Influenza A (1) and, B (1).
[b]Chronic rhinitis (5), arrhythmia (1).
[c]Tonsillectomy (3), surgery for nasal septum (1).
N, number.

Table 2. Attack rates and relative risks associated with the adenovirus respiratory infection in the outbreak

Variables	Subjects (N)	Cases (N)	AR	RR	95% CI	*P* value+
Retrospective investigation of members of departments using the swimming pool (Study 1)						
Overall	59	33	55.9	-	-	-
High incidence grade of the school (1)						
High school 3rd grade	9	8	88.9	1.78	1.24–2.55	0.06
Others	50	25	50.0	Ref		
High incidence grade of the school (2)						
High school 1st grade	12	8	66.7	1.25	0.77–2.03	0.52
Others	47	25	53.2	Ref		
High incidence athletic department						
Swimming	39	26	66.7	1.90	1.01–3.60	0.03
Others	20	7	35.0	Ref		
Sharing the dormitory room with the case before the symptom onset						
Yes	39	17	43.6	0.73	0.50–1.07	0.14
No	20	16	80.0	Ref		
Prospective surveillance of the entire members of the physical education school (Study 2)						
Overall	362	14	3.9	-	-	-
High incidence grade of the school						
High school 1st grade	66	9	13.6	8.07	2.80– 23.31	<0.001
Others	296	5	1.7	Ref		
High incidence athletic department						
Shooting	21	6	28.6	12.18	4.65– 31.88	<0.001
Others	341	8	2.3	Ref		
Sharing the dormitory room with the case before the symptom onset						
Yes	51	5	9.8	3.39	1.18–9.70	0.03
No	311	9	2.9	Ref		

N, number; AR, attack rate; RR, relative risk; CI, confidence interval; Ref, reference; +, Fisher's exact test using two-tailed *P*-values.

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Table 3. Multivariable logistic regression of potential risk factors for adenovirus respiratory infection in the prospective surveillance of the entire members of the physical education school

Variables	Adjusted OR	95% CI	*P* value
Athletic department of shooting	20.70	4.90–87.47	<0.001
High school, 1st grade	10.95	2.90–41.33	<0.001
Sharing the dormitory room with the case	1.20	0.28–5.11	0.81

OR, odds ratio; CI, confidence interval.

5. Results of environmental investigation

The swimming pool water was filtered using a circular filtration system, and an automatic chlorine injection system was implemented. The concentration of free residual chlorine in the water was 0.5 ppm, meeting the requirement of the related regulation. No adenovirus was detected in the pool water and the surfaces of locker rooms and shower rooms where frequent contacts happen.

Two to four students were sharing dormitory rooms based on their athletic department. No adenovirus was detected in the surfaces of the shower rooms, door knobs, and shelves where frequent contacts happen.

6. Infection control measures

The students of the swimming department have continued with their training on school without returning home on weekends to prepare for a swimming competition and continued with their school activities even during periods of respiratory symptoms. Restriction of school activities and returning home were recommended to prevent transmission between the students as an infection control measure. For 5 days, from Jun 3 to 7, all students returned home and the school was temporarily closed. 11 days after temporary closure of School J, the last confirmed case occurred on June 18, and the outbreak was over (**Fig. 1**). The number of school days during 7days after symptom onset [22], decreased from 3.08 days to 1.17 days after intervention, but there was no statistically significant difference ($P = 0.053$).

Use of the swimming pool was suspended and disinfection was conducted to prevent a transmission through the environment. When the suspected cases were identified, additional disinfection was conducted to the dormitory room of the cases. During the temporary school closure period, the entire environment of school was cleaned and disinfected.

Education regarding infection control measures such as hand hygiene, cough etiquette, and use of personal equipment was provided to the students and their families.

DISCUSSION

A total of 47 suspected cases of acute respiratory infection caused by adenovirus were identified in a physical education school in 2017. Of them, 18 tested positive for adenovirus, and the gene analysis on the adenoviruses showed that the sequence was 100% identical in homology and the type was confirmed to be HAdV B-55. Outbreak of HAdV B-55 acute respiratory infection had been reported in physical training facilities and hospital in China [4, 5] and in a military camp in Korea [20]. This study is the first to report on the outbreak of HAdV B-55 acute respiratory infection in communities, except military camps.

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HAdV B-55 is a newly named virus and known as the recombination of types B-11 and B-14[23]. The analysis on the HAdV B-14 acute respiratory infection that occurred in the 4 states of the US showed a case fatality rate of 5% [19]. It has been reported that HAdV B-55 caused severe pneumonia in among the members of the Korean military. The physical education School J had some similarities with military camps: all students are accommodated in a dormitory, sometimes stayed during weekends to attend trainings, and performed lots of physical activities. Although none of them developed pneumonia, 32.6% were hospitalized. There are some opinions that overcrowding or increased physical and psychological stress is one of the factors for the of HAdV B-55 infection among adults [4, 24]. Therefore, HAdV B-55 is considered as a possible causal pathogen when the acute respiratory infection outbreak occurred in those settings.

This epidemic lasted for 56 days (from April 24 to Jun 18, 2017), and the epidemic curve showed a trend of propagated transmission. The interval between the peak in the epidemic curve was 2-9 days, which was similar to the incubation period of acute respiratory infection caused by adenovirus (2-14 days) [2, 3].

This epidemic was initiated in student of the modern sports department using the swimming pool, spread in the swimming department, and transmitted to other students in other departments who were not using the swimming pool (**Fig. 2**). In the univariate analysis of Study 1, it was identified that the attack rate was significantly higher in the swimming group (**Table 2**). In the multivariable analysis of Study 2, being a member of the shooting department and being a first grade student of high school were identified as independent risk factors (**Table 3**). Sharing a dormitory room was also assumed to have contributed to the transmission of the infection, but it was not identified as an independent risk factor. Therefore, it was presumed that the propagation mostly occurred during the performance of activities held by each athletic department, while some propagation occurred during class activities.

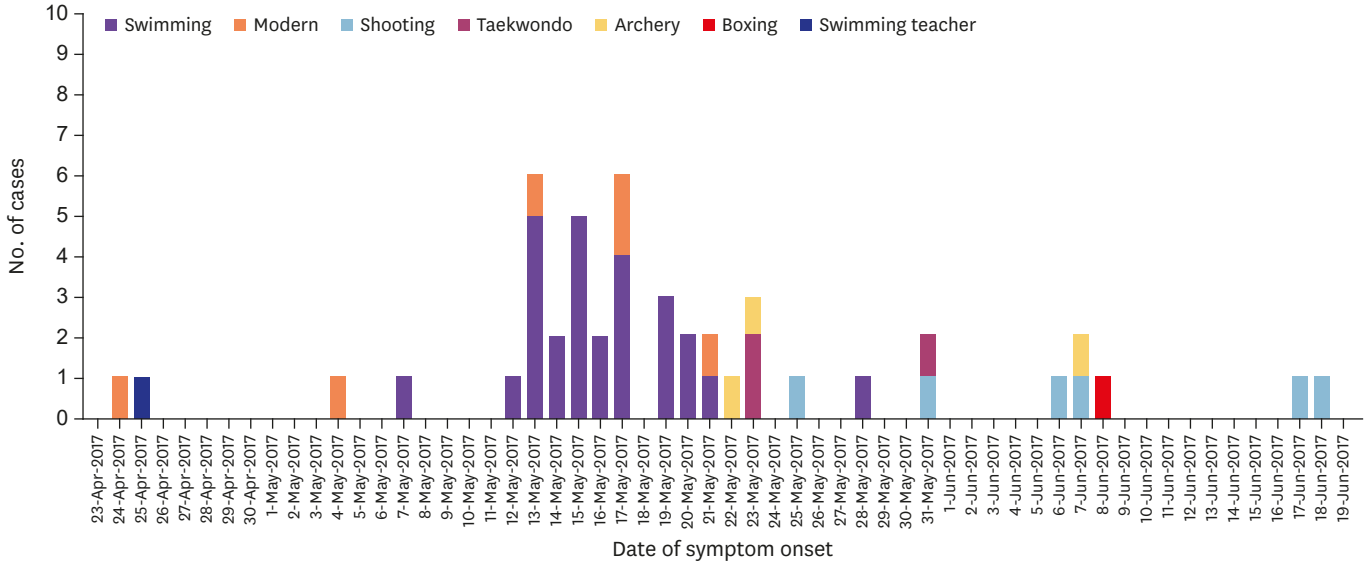

Figure 2. Epidemic curve of the outbreak by the athletic departments.

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Adenovirus is transferred via contacts, droplet, and exposure to contaminated environments [10, 11]. In this investigation, infection control measures were applied on two infection transmission routes. To prevent the propagated transmission, suspected cases were asked to go home and temporary school closure was carried out. To prevent the environmental transmission, disinfection was conducted using with high concentration chlorine disinfectant.

A few clinical characteristics of the HAdV B-55 acute respiratory infection cases could be identified through this study. The most common symptoms among 18 confirmed cases of adenovirus infection by PCR tests were fever and headache (83.3%, respectively), and sore throat (66.7%). These symptoms were similar to those reported in previous studies. However, headache (83.3%) was higher than that reported in China (25.6%), and cough (16.7%) was lower than that reported in Korean military (83.3%, 94.6%) [5, 20]. Diarrhea appeared 27.8% of the confirmed cases, which was similar to that reported in the Korean military (12.8%, 33.8%) [20]. Eye congestion appeared 27.8% of the confirmed cases. Approximately 44.4% of confirmed cases were hospitalized, which was lower than the rate reported in the Korean military (62.0%) [20].

This study had several limitations. First, selection bias could potentially occur. The initial investigation was performed on all students and teachers who had been using the swimming pool. But for the students and teachers who did not use the pool, the investigation was performed only on those who showed symptoms of the respiratory infection on the prospective surveillance. Thus, there is a possibility that a thorough investigation has not been conducted on non-users of the swimming pool. Second, there is a possibility of information bias because the epidemiological investigation started about 1 month after the outbreak. In order to minimize the bias, face-to-face interviews were conducted for a considerable amount of time. In cases of hospital admission, medical records were investigated. Third, there is a possibility of misclassification, because the possibility of infection from other pathogens among the initial suspected case could not be excluded.

The sources of respiratory infection are not easy to determine during outbreak due to the relatively long incubation period and the complicated transmission routes affected both by human and environmental factors. Therefore, to identify the cause and the transmission routes, it is necessary to perform systematic investigation at the initiation of the investigation, and to identify the characteristics of the epidemic via in-depth investigation on the initial cases.

In conclusion, 18 confirmed adenovirus respiratory infection cases and 29 suspected cases were identified in one physical education school in Korea. Our results suggest that infection initiated in users of swimming pool had transmitted to other students through the school activities held by athletic department and class. The continued performance of school activities without restrictions by those students with respiratory symptoms could have caused the outbreak. Therefore, infection control measures such as early detection of symptoms of respiratory infection and restriction of group activity are necessary to prevent the respiratory infection outbreak in communal living setting.

Even though HAdV B-55 has been recently reported as the pathogenic organism of respiratory infection outbreak or severe cases, the characteristics of acute respiratory infection caused by HAdV B-55 are not well explored in Korea. This study has contributed to identifying the clinical and epidemiological characteristics of HAdV B-55 and will be the basis for further research in the future.

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