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<THE TOPIC OF THIS MONTH> Adenovirus infections, 2008 to 2020, Japan

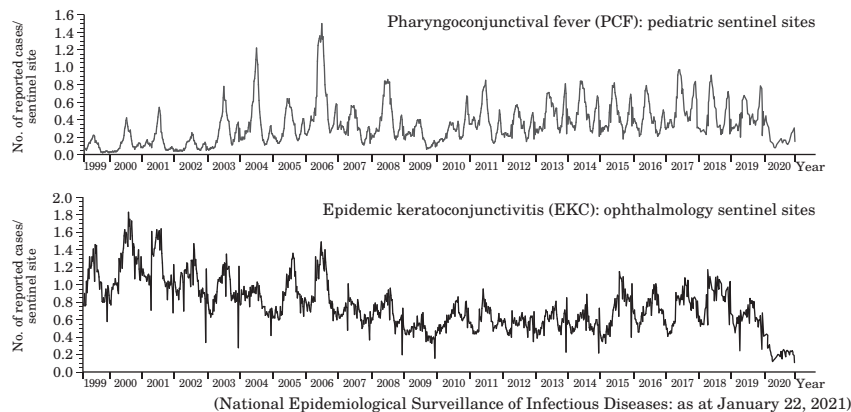
Table 1. Adenovirus species and key associated diseases, by type

Species	Key associated diseases	Major adenovirus types	Minor adenovirus types
A	Infectious gastroenteritis	12, 31	61
B	ARI, PCF, EKC, HC	3, 7, 11, 34, 35	14, 16, 55, 66, 68, 79
C	ARI, PCF	1, 2, 5, 6	57
D	EKC, urethritis	8, 64(19a)*, 37, 53, 54, 56, 85	81
E	ARI, EKC, PCF	4	-
F	Infectious gastroenteritis	40, 41	-
G	Infectious gastroenteritis	52	-

ARI : acute respiratory infection, PCF : pharyngoconjunctival fever,
EKC : epidemic keratoconjunctivitis, HC : hemorrhagic cystitis

*19a reclassified as 64

Figure 1. Weekly number of reported cases per sentinel, week 14, 1999 to week 53, 2020, Japan



(National Epidemiological Surveillance of Infectious Diseases: as at January 22, 2021)

Human mastadenoviruses (Ad), which belong to the genus Mastadenovirus in the family Adenoviridae, are non-enveloped double-stranded DNA viruses that are relatively physicochemically stable. Ads are currently grouped into seven species from A to G and over 80 types have been described (as an example, type 3 is denoted as Ad3). Ads have been reported as serotypes up to Ad51, but those classified after Ad52 have been reported as genotypes based on whole genome sequencing.

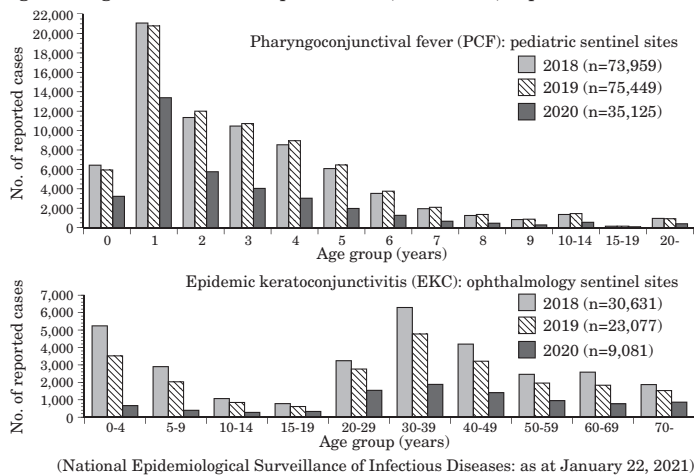
Ad infection is associated with respiratory diseases, such as ARI (acute respiratory infections), ocular diseases, such as EKC (epidemic keratoconjunctivitis), and gastrointestinal diseases such as infectious gastroenteritis. Ads are also associated with urological diseases, such as hemorrhagic cystitis and urethritis, along with hepatitis (Table 1 and Table 2 in p.69 and see p.70 of this issue). The epidemic trajectory and inflammatory response vary depending on the Ad species (Nakamura *et al.*: JMV2018).

Ad infections are monitored under the National Epidemiological Surveillance of Infectious Diseases (NESID) system, specifically via sentinel surveillance for pharyngoconjunctival fever (PCF) and infectious gastroenteritis at approximately 3,000 pediatric sentinel sites nationwide and for EKC at approximately 700 ophthalmology sentinel sites nationwide (for notification criteria, see <https://www.mhlw.go.jp/bunya/kenkou/kekkaku-kansenshou11/01-05-16.html>, <https://www.mhlw.go.jp/bunya/kenkou/kekkaku-kansenshou11/01-05-30.html>). The notification criteria for EKC were revised in April 2020 and the pathogenic virus was defined as Ad, with more detailed aspects included in the definition (see p.71 of this issue). Laboratory-based surveillance is also being performed (see p.72 of this issue).

Reported cases of PCF and EKC: Since reporting of PCF cases at pediatric sentinel sites began in 1987, the largest number of PCF cases was reported in 2006 (Fig. 1, top). Although a summer peak in notifications has been consistently observed, an additional peak in winter has also been observed since 2003 (<https://www.niid.go.jp/niid/en/10/2096-weeklygraph/1645-02pcf.html>, <https://nesid4g.mhlw.go.jp/Byogentai/Pdf/data27e.pdf>). In 2020, during the coronavirus disease 2019 (COVID-19) epidemic, summer and winter peaks were also observed, although they were low (Fig. 1, top). Among PCF patients, children one year of age are reported in large numbers (Fig. 2 in p.68, top).

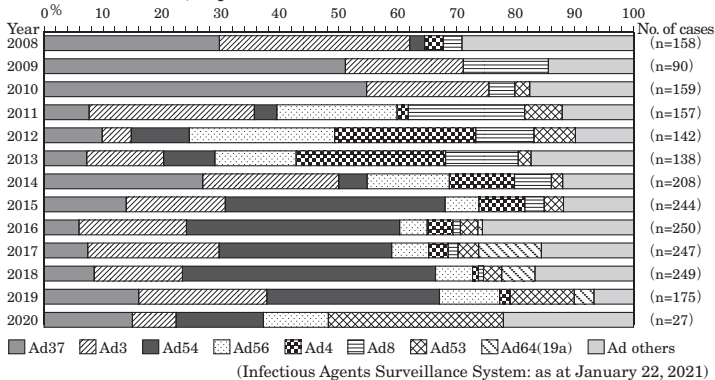
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Figure 2. Age distribution of reported cases, 2018-2020, Japan



(National Epidemiological Surveillance of Infectious Diseases: as at January 22, 2021)

Figure 3. Adenovirus types detected from epidemic keratoconjunctivitis cases, 2008-2020, Japan



(Infectious Agents Surveillance System: as at January 22, 2021)

gastroenteritis was 3,751 and the main pathogen was species F (Ad40 or 41) (Table 2 in p.69). There were also 143 detections of Ad31 belonging to species A (see p.75 of this issue).

Ad7 belonging to species B is known to cause severe pneumonia. During 1995-1998, when Ad7 was circulating at a high level, 863 cases of Ad7 detection were reported (<https://www.niid.go.jp/niid/images/iasr/table/virus/adv91-00.pdf>) and several fatal cases of Ad7 infection were also reported (IASR 17: 99-100, 1996 & 18: 79-80, 1997). During 2008-2020, 46 cases of Ad7 detection were reported (Table 2 in p.69); continued careful monitoring of Ad7 is warranted (see p.76 of this issue).

Laboratory diagnostic methods: Although the lateral flow test to detect Ad antigen (IC-kit) cannot discriminate Ad types, it has the advantage of providing rapid results in the clinical setting. In Japan, approximately 2,700,000 kits are utilized annually, and with improvements, the sensitivity has been increasing.

Currently, typing has shifted from serotyping to genotyping. For routine laboratory testing at PHIs, partial sequencing of the penton base, hexon, and fiber regions is carried out (Laboratory manual for the diagnosis of PCF and EKC, ed. 3, https://www.niid.go.jp/niid/images/lab-manual/adeno_v3.pdf). As adenoviruses frequently undergo recombination among different types within a species, sequencing of multiple regions is necessary (see p.78 of this issue).

Therapy and prevention: Currently, there are no specific antiviral agents available in Japan that can be used to treat Ad infection. It is important to strengthen activities, such as the development of therapeutics against Ad infection, because it can be fatal in immunosuppressed patients after organ transplantation (see p.70 of this issue).

As Ad is transmitted via contact or droplets, hand hygiene is important for infection prevention. However, standard alcohol-based disinfectants are ineffective and utilization of an effective disinfectant is important (see p.75 of this issue). In particular, as the eye discharge and tears of infected patients contain large amounts of Ad, it is important in ophthalmology to detect infected patients early and reduce further transmission through patient interviews and diagnostic kits in accordance with the guidelines for ophthalmologists (<https://www.nichigan.or.jp/member/journal/guideline/detail.html?ItemId=283&dispMid=909>). For children, hygiene management should be implemented following the School Health and Safety Act and the Infection Control Guidelines in Nurseries (<http://www.mhlw.go.jp/stf/seisakunitsuite/bunya/0000123472.html>) to target the source of infection, route of transmission, and susceptibility (the three major factors for the establishment of infection).

Although Ad is often regarded as a mild pediatric infectious disease, it can cause a wide range of diseases depending on the species and type. Furthermore, as it can be severe, infection control is important.

In contrast, EKC patients monitored at ophthalmology sentinel sites have been reported most frequently during May-August. Since 2015, however, notifications increased through autumn (Fig. 1 in p.67, bottom and <https://www.niid.go.jp/niid/ja/10/2096-weeklygraph/1656-15ekc.html>). EKC patients are children, mainly among those aged 0-4 years, and adults across a wide age range, mainly in their 30s (Fig. 2, bottom).

According to an analysis using data from the National Database of Health Insurance Claims and Specific Health Checkups of Japan, the number of PCF and EKC patients in Japan during 2012-2016 was approximately 100,000 and 500,000-750,000 per year, respectively (see p.73 of this issue).

Isolation/detection of Ad: From 2008 to 2020, prefectural and municipal public health institutes (PHIs) reported 20,499 cases of the isolation/detection of Ad (Table 2 in p.69), with Ad2 being the most frequent (26%), followed by Ad3 (19%) and Ad1 (14%).

The number of Ad isolation/detection reports from PCF patients was 3,597, with Ad3, Ad2, Ad1, Ad4, and Ad5 being frequent (Table 2 in p.69).

From EKC patients, a total of 2,244 cases of Ad isolation/detection were reported; species D Ads, including Ad54, Ad37, Ad8, Ad53, and Ad64 (19a), were frequently reported (Table 2 in p.69). Ad85 found in Japan is also the cause of EKC (Kaneko: JJID2020). In addition, Ad3 of species B and Ad4 of species E were reported from EKC patients (Fig. 3 and Table 2). In 2020, the notification criteria for EKC in NESID were revised, and EKC was defined as being caused by species D Ads.

In other countries, Ad8 is the major pathogen of EKC, but in Japan, the frequency of Ad8 detection has decreased, whereas that of Ad54 detection has increased in recent years (Table 2 in p.69).

The number of Ad reports from patients with infectious gastroenteritis was 3,751 and the main pathogen was species F (Ad40 or 41) (Table 2 in p.69). There were also 143 detections of Ad31 belonging to species A (see p.75 of this issue).

The statistics in this report are based on 1) the data concerning patients and laboratory findings obtained by the National Epidemiological Surveillance of Infectious Diseases undertaken in compliance with the Act on the Prevention of Infectious Diseases and Medical Care for Patients with Infectious Diseases, and 2) other data covering various aspects of infectious diseases. The prefectural and municipal health centers and public health institutes (PHIs), the Department of Environmental Health and Food Safety, the Ministry of Health, Labour and Welfare, and quarantine stations, have provided the above data.

(THE TOPIC OF THIS MONTH-Continued)

Table 2. Number of adenovirus isolation/detection, by year and clinical diagnosis, 2008-2020, Japan

Adenovirus Species	Year												Total	Major clinical diagnosis				
	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019		2020	PCF	Infectious gastroenteritis	EKC	LRI
Ad 1	195	205	228	260	240	252	237	213	205	256	235	240	74	470	351	10	280	802
Ad 2	412	387	471	385	511	447	399	387	462	505	495	405	145	988	746	16	458	1,525
Ad 3	431	154	306	474	131	238	397	322	367	379	345	341	55	1,468	202	437	180	868
Ad 4	23	5	2	13	102	154	101	101	85	31	16	18	1	218	31	143	20	116
Ad 5	146	93	139	103	129	107	90	105	93	123	117	81	37	193	200	5	117	396
Ad 6	33	29	35	32	43	32	60	24	34	34	20	24	6	47	59	2	45	80
Ad 7	26	2	2	-	2	1	-	-	-	2	2	9	-	7	2	6	5	9
Ad 8	6	13	7	32	15	17	14	9	4	4	6	-	-	2	1	117	-	1
Ad 9	-	-	-	2	-	-	-	-	1	-	-	-	-	-	-	3	-	-
Ad 11	17	3	6	5	3	2	4	2	3	4	2	1	2	4	-	11	1	1
Ad 12	-	-	-	1	-	1	1	-	-	-	-	-	-	-	3	-	-	-
Ad 13	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1	-	-
Ad 15	-	2	1	-	-	-	-	-	-	-	-	-	-	-	-	2	1	-
Ad 19	5	-	1	1	1	2	4	5	25	4	2	-	1	2	-	42	-	-
Ad 21	-	-	-	-	-	-	-	-	1	2	-	-	-	-	-	-	-	-
Ad 31	10	10	27	20	26	29	16	11	14	20	18	14	4	-	143	-	3	3
Ad 33	-	-	-	-	1	-	-	1	-	-	-	-	-	-	-	2	-	-
Ad 34	1	-	-	1	-	-	-	-	-	-	-	-	-	-	-	1	-	-
Ad 35	-	-	-	1	-	-	1	-	1	-	1	-	-	-	-	1	-	-
Ad 37	55	49	102	15	18	12	66	44	20	19	22	35	5	8	1	392	-	3
Ad 40	-	-	-	2	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Ad 41	39	45	59	64	90	70	74	91	120	141	130	136	17	4	966	-	7	2
Ad 40/41†	50	58	86	46	64	34	34	60	25	42	25	24	3	-	534	-	2	-
Ad 46	-	-	-	-	-	-	-	-	1	-	-	1	-	-	-	2	-	-
Ad 53	-	-	4	11	10	3	5	8	9	9	8	21	10	1	-	90	-	-
Ad 54	4	-	-	7	15	14	15	104	103	91	128	54	4	36	3	461	6	1
Ad 56	-	-	-	35	51	32	33	17	12	20	20	32	4	4	3	194	-	1
Ad 64 (19a)	-	-	-	-	-	-	-	-	2	33	15	7	2	3	-	48	1	-
Ad others	-	-	-	-	-	-	6	2	2	1	17	2	-	3	1	22	1	-
Ad NT	259	226	286	178	157	190	254	257	128	130	102	107	20	139	504	236	258	343
Total	1,713	1,281	1,762	1,688	1,609	1,637	1,811	1,763	1,717	1,850	1,726	1,552	390	3,597	3,751	2,244	1,385	4,151

(Infectious Agents Surveillance System: as at January 22, 2021)

NT: Not typed

PCF: pharyngoconjunctival fever, EKC: epidemic keratoconjunctivitis, LRI: lower respiratory infection, URI: upper respiratory infection

† Ad 40/41 is considered directly from feces by ELISA kit in which Ad 40 and 41 can not be distinguished from each other.