previous reports [20]. To our knowledge, this is the second report of USA300 being isolated in Japan; the first case was a 3-month-old girl born in the USA who subsequently moved to Japan [15]. Our patient was an American woman who came to Japan from the USA more than 1 year earlier. Thus, the strains in the two cases may have originated in the USA. However, the husband of our patient works for the US Navy in Japan, and as soldiers are thought to be at increased risk of CA-MRSA infection [8], transmission from her husband is also possible. He has not yet exhibited signs of CA-MRSA infection, but colonization was not examined.

Epidural abscess is a suppurative infection occurring in the potential space between the inner skull table and dura mater. *Staphylococcus aureus* is responsible for two thirds of cases, with the incidence of MRSA increasing in recent years [24]. Epidural abscess is one of the most dire consequences of metastatic bacteremia, frequently resulting in paralysis [25], and usually develops as a complication of craniotomy or compound skull fracture or in patients with implantable spinal or vascular devices. Thus, it rarely occurs in healthy people living in community settings. However, our patient had no past history of cranial surgery or treatment with implantable devices. As she suffered from subcutaneous infection a few weeks earlier, the possible pathway of transmission to intracranial lesion was via the bloodstream from skin lesions. Two cases of epidural abscess caused by CA-MRSA have been reported in the USA [26, 27], and similarly to this case, the primary lesion was thought to be soft-tissue lesions in these two cases. Although they improved after administration of antibiotics for 6–8 weeks, we performed surgical drainage after 1-week administration of antibiotics, as MRI showed no improvement.

Here, we report the first case in Japan of epidural abscess caused by the USA300 strain. The number of CA-MRSA isolates has been increasing in Japan, and this study provides a warning that CA-MRSA originating from other countries may be introduced into Japan and that infections such as epidural abscess caused by CA-MRSA should be considered in the differential diagnoses of healthy patients with persistent headache accompanied by skin lesions.

References

1. Moran GJ, Krishnadasan A, Gorwitz RJ, Fosheim GE, McDougal LK, Carey RB, et al. Methicillin-resistant *S. aureus* infections among patients in the emergency department. N Engl J Med. 2006;355:666–74.
2. Miller LG, Perdreau-Remington F, Rieg G, Mehdi S, Perlroth J, Bayer AS, et al. Necrotizing fasciitis caused by community-associated methicillin-resistant *Staphylococcus aureus* in Los Angeles. N Engl J Med. 2005;352:1445–53.
3. Valentini P, Parisi G, Monaco M, Crea F, Spanu T, Ranno O, et al. An uncommon presentation for a severe invasive infection due to methicillin-resistant *Staphylococcus aureus* clone USA300 in Italy: a case report. Ann Clin Microbiol Antimicrob. 2008;7:11.
4. Okuma K, Iwakawa K, Turnidge JD, Grubb WB, Bell JM, O'Brien FG, et al. Dissemination of new methicillin-resistant *Staphylococcus aureus* clones in the community. J Clin Microbiol. 2002;40:4289–94.
5. Deurenberg RH, Vink C, Kalenic S, Friedrich AW, Bruggeman CA, Stobberingh EE. The molecular evolution of methicillin-resistant *Staphylococcus aureus*. Clin Microbiol Infect. 2007;13:222–35.
6. David MZ, Mennella C, Mansour M, Boyle-Vavra S, Daum RS. Predominance of methicillin-resistant *Staphylococcus aureus* among pathogens causing skin and soft tissue infections in a large urban jail: risk factors and recurrence rates. J Clin Microbiol. 2008;46:3222–7.
7. Kazakova SV, Hageman JC, Matava M, Srinivasan A, Phelan L, Garfinkel B, et al. A clone of methicillin-resistant *Staphylococcus aureus* among professional football players. N Engl J Med. 2005;352:468–75.
8. Campbell KM, Vaughn AF, Russell KL, Smith B, Jimenez DL, Barrozo CP, et al. Risk factors for community-associated methicillin-resistant *Staphylococcus aureus* infections in an outbreak of disease among military trainees in San Diego, California, in 2002. J Clin Microbiol. 2004;42:4050–3.
9. Maree CL, Daum RS, Boyle-Vavra S, Matayoshi K, Miller LG. Community-associated methicillin-resistant *Staphylococcus aureus* isolates causing healthcare-associated infections. Emerg Infect Dis. 2007;13:236–42.
10. Seybold U, Kourbatova EV, Johnson JG, Halvosa SJ, Wang YF, King MD, et al. Emergence of community-associated methicillin-resistant *Staphylococcus aureus* USA300 genotype as a major cause of health care-associated blood stream infections. Clin Infect Dis. 2006;42:647–56.
11. McDougal LK, Steward CD, Killgore GE, Chaitram JM, McAllister SK, Tenover FC. Pulsed-field gel electrophoresis typing of oxacillin-resistant *Staphylococcus aureus* isolates from the United States: establishing a national database. J Clin Microbiol. 2003;41:5113–20.
12. Boyle-Vavra S, Daum RS. Community-acquired methicillin-resistant *Staphylococcus aureus*: the role of Panton–Valentine leukocidin. Lab Invest. 2007;87:3–9.
13. Larsen A, Stegger M, Goering R, Sorum M, Skov R. Emergence and dissemination of the methicillin resistant *Staphylococcus aureus* USA300 clone in Denmark (2000–2005). Euro Surveill 2007;12.
14. Gottlieb T, Su WY, Merlino J, Cheong EY. Recognition of USA300 isolates of community-acquired methicillin-resistant *Staphylococcus aureus* in Australia. Med J Aust. 2008;189:179–80.
15. Shibuya Y, Hara M, Higuchi W, Takano T, Iwao Y, Yamamoto T. Emergence of the community-acquired methicillin-resistant *Staphylococcus aureus* USA300 clone in Japan. J Infect Chemother. 2008;14:439–41.
16. Enright MC, Day NP, Davies CE, Peacock SJ, Spratt BG. Multilocus sequence typing for characterization of methicillin-resistant and methicillin-susceptible clones of *Staphylococcus aureus*. J Clin Microbiol. 2000;38:1008–15.
17. Fey PD, Said-Salim B, Rupp ME, Hinrichs SH, Boxrud DJ, Davis CC, et al. Comparative molecular analysis of community- or hospital-acquired methicillin-resistant *Staphylococcus aureus*. Antimicrob Agents Chemother. 2003;47:196–203.
18. Ito T, Katayama Y, Asada K, Mori N, Tsutsumimoto K, Tiensasitorn C, et al. Structural comparison of three types of

staphylococcal cassette chromosome *mec* integrated in the chromosome in methicillin-resistant *Staphylococcus aureus*. Antimicrob Agents Chemother. 2001;45:1323–36.
19. Clinical and Laboratory Standards Institute. Performance standards for antimicrobial susceptibility testing; 19th informational supplement, vol. 29, no. 3, M100–S19. Wayne, PA: Clinical and Laboratory Standards Institute; 2009.
20. Tenover FC, McDougal LK, Goering RV, Killgore G, Projan SJ, Patel JB, et al. Characterization of a strain of community-associated methicillin-resistant *Staphylococcus aureus* widely disseminated in the United States. J Clin Microbiol. 2006;44:108–18.
21. Perez-Roth E, Claverie-Martin F, Villar J, Mendez-Alvarez S. Multiplex PCR for simultaneous identification of *Staphylococcus aureus* and detection of methicillin and mupirocin resistance. J Clin Microbiol. 2001;39:4037–41.
22. Schmitz FJ, Sadurski R, Kray A, Boos M, Geisel R, Kohrer K, et al. Prevalence of macrolide-resistance genes in *Staphylococcus aureus* and *Enterococcus faecium* isolates from 24 European university hospitals. J Antimicrob Chemother. 2000;45:891–4.
23. Johnson JK, Khoie T, Shurland S, Kreisel K, Stine OC, Roghmann MC. Skin and soft tissue infections caused by methicillin-resistant *Staphylococcus aureus* USA300 clone. Emerg Infect Dis. 2007;13:1195–200.
24. Darouiche RO. Spinal epidural abscess. N Engl J Med. 2006;355:2012–20.
25. Rubinstein E. *Staphylococcus aureus* bacteraemia with known sources. Int J Antimicrob Agents. 2008;32(Suppl 1):S18–20.
26. Lo BM, Erwin EA. Missed epidural brain abscess after furunculosis. Am J Emerg Med. 2008;26:522 e3–4.
27. Bruns AS, Sood N. Community-acquired methicillin-resistant *Staphylococcus aureus* epidural abscess with bacteremia and multiple lung abscesses: case report. Am J Crit Care. 2009;18(88):86–7.

Review:

Severe Acute Respiratory Syndrome (SARS)

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[Received December 16, 2010; accepted January 5, 2011]

Severe acute respiratory syndrome, or SARS, was the first emerging infection of the 21st century. Severe pneumonia is the main symptom, and the case fatality rate was about 10%. In general, convalescence becomes less satisfactory with the age of the patient. The older the patient is, the more unsatisfactorily his or her convalescence is. The disease is transmitted mainly through the spread of droplets from the human respiratory tract. Many health care professionals became infected with SARS within the medical facilities in which they worked. No peculiar medicine or vaccine for SARS has yet been developed. A worldwide epidemic of SARS centered in China broke out around during the period from 2002 to 2003; about 8,000 cases were recorded. Although this epidemic has come to an end, attention should be paid to SARS because of its possible reemergence. Preparedness for SARS can be also applied to measures against other emerging infections.

Keywords: severe acute respiratory syndrome (SARS), coronavirus, emerging infection, acute respiratory distress syndrome (ARDS), measure against infection

1. Introduction

In 2003, the severe acute respiratory syndrome, or SARS, suddenly became the world's first emerging infection of the 21st century. The disease is transmitted by a virus and causes severe pneumonia as the main symptom. SARS spread worldwide in a short period, but the epidemic came to an end about 9 months after its outbreak. Nearly 8 years have passed since then, and no further patients have been reported, except for some special cases, including cases of leakage from laboratories. However, attention should still be paid to SARS because of its possible reemergence. The experience that was gained from the epidemic of SARS is precious, and a further review of SARS would be helpful in determining measures against other emerging infections. In fact, the experience gained in combating the epidemic of SARS has been referred to in considering measures against novel influenzas. This paper summarizes the SARS epidemic mainly from a clinical viewpoint.

2. Review of 2003 Epidemic

The disease which would later be named the severe acute respiratory syndrome, or SARS, was initially recognized in mid-November, 2002 in the city of Foshan, Guangdong Province, China. The disease was at first considered to be an infection, the main symptoms of which were fever, headache, various symptoms of the respiratory organs, and pneumonia. The disease-causing microbe was yet unknown [1]. On 11 February 2003, the Chinese authorities published the facts of the disease to the world for the first time, reporting that "305 cases of the disease have occurred in Guangdong Province, 5 of them fatal. The epidemic is being brought under control."

On 21 February, 10 days after this publication, however, the following incident occurred: when a 64-year-old doctor who had been infected with this disease in Guangdong Province stayed on the 6th floor of the "M" Hotel in Hong Kong, 16 guests, many of whom were staying on the same floor as the doctor, became infected. Many of these virus carriers flew back to their home countries, e.g., the United States, Singapore, Canada, Vietnam and others, and the infection soon began spreading worldwide [2]. Some of the victims were also hospitalized in Hong Kong, triggering an explosive outbreak there.

Responding to the emergence of the novel infection, the cause of which was still unknown, the World Health Organization, WHO, issued on 12 March 2003 a global alert against travel to areas experiencing the epidemic. In that stage, the infection was named SARS, and the medical research institutions of the world undertook to identify the pathogen of the disease. Late in March, soon after the issuance of a global alert, it was reported that the pathogen of SARS was SARS-coronavirus, referred to hereinafter as SARS-CoV [3-5].

There have been various incidents since then. For example, more than 300 residents were infected with SARS at the "Amoy Garden Complex" high-rise condominium in Hong Kong. SARS also reemerged in Canada, where the infection had once seemed to have ceased to exist. However, the measures to contain the virus, quarantine patients, and prevent infections were effective, so the spread of infection lost momentum around June of the same year. Finally, on 5 July, WHO lifted the designation of Taiwan as the last remaining "epidemic area"

and officially declared the end of the worldwide epidemic of SARS. According to WHO's statistics [6], a total of 8,096 patients infected with SARS were reported in 26 countries during the 9-month period from November 2002 to July 2003, including 774 fatalities. According to WHO's statistics, the case fatality rate of SARS was as high as 9.6%. Among the countries concerned, many cases were reported from Mainland China (5,327 patients), Hong Kong (1,755), Taiwan (346), Singapore (238), and Canada (251). The most significant epidemic areas were located in Asia.

In Japan on 3 April 2003, the Ministry of Health, Labor, and Welfare designated SARS an "emerging infection" based on the Infectious Disease Control Law and took appropriate measures, such as obligatory reporting, mandatory hospitalization, tightening of the quarantine system, and recommending that travel be deferred to epidemic areas. Only SARS has been designated an "emerging infection" since the enactment of the Infectious Disease Control Law in Japan. An incident was reported in May of the same year: a Taiwanese doctor who had visited the Kansai region of Japan as a tourist was later found to be infected with SARS. Miraculously, no SARS patients were reported until the official declaration of the end of worldwide epidemic of SARS. Later, SARS was put under the legal category of "First rate infectious disease" through an amendment of the Infectious Disease Control Law in 2003, and it was classified as a "Second rate infectious disease" by a further amendment of the law in 2007.

3. SARS-CoV

The pathogen of SARS is SARS-CoV, which belongs to the family Coronaviridae [3-5]. The coronaviruses have been divided into three distinct antigenic groups. Group I contains the human coronavirus 229E and a number of animal coronaviruses. Group II contains the human coronavirus OC43 and several animal coronaviruses, and group III contains a number of avian coronaviruses. The SARS-CoV is, based on genetic sequence studies, distantly related to all three above-mentioned groups and may be classified under a fourth group [7].

The ancestor virus of SARS-CoV is thought to have originated in wild animals. Initially, the masked palm civet (*Paguma larvata*) was suspected to be a natural host of SARS-CoV. This hypothesis based on the following facts: a virus similar to human SARS-CoV was detected in a masked palm civet marketed in Guangdong Province, China, where SARS originated, and the antibody titer against SARS-CoV of the traders who dealt in the animals marked high values. Later, it was found out that SARS-CoV can also be transmitted to other animals, such as ferrets and cats, and the masked palm civet is now thought, based on the genetic analysis of the virus, to have been infected with the virus by chance.

In September 2005, Lau et al. in Hong Kong [8] and Li et al. in Peking [9] reported almost at the same time that genes extremely similar to those of the virus SARS-CoV had been detected in a wild horseshoe bat (*Rhinolophus*), indicating the virus of this bat could be the ancestor of SARS-CoV. It is suspected that SARS originally existed in bats and happened to come into the human world.

4. Pathology and Patients' Conditions

The lung can be the organ most damaged by SARS, and, seen from the clinical viewpoint, conditions similar to those of ARDS, or acute respiratory distress syndrome, develop in many cases. Autopsy findings of lungs showed increases in weight, edema, and hemorrhagic infarct. From a histological viewpoint, various observations ranging from the exudative stage to the organization stage of diffuse alveolar damage (DAD) can be made. Pulmonary edema, the formation of a hyaline membrane, the separation of alveolar epithelium, and the infiltration of macrophage, neutrophil, and lymphocyte can be seen. According to the findings of the study using in situ hybridization, in the cases in which patients died within 10 days after the onset of illness, the nucleic acid of SARS-CoV reacted positive in alveolar epithelium, a part of epithelium of respiratory bronchioles, and alveolar macrophage, while in the cases in which patients died 20 days and over after the onset of illness, it reacted negative [10]. These findings are indicative in reviewing the period of infectiousness of SARS.

As for other human organs other than the lungs, nonspecific changes can be found in the liver, spleen, lymph nodes, and kidneys. Infection with SARS-CoV was also confirmed in the cells of the intestinal epithelium.

Li et al. [11] reported that the angiotensin-converting enzyme 2 (ACE2) would function as a receptor of human cells for SARS-CoV. In fact, ACE2 appears remarkably in human bronchi, the alveolus, kidneys, and the digestive tract. Accordingly, going on the hypothesis that SARS-CoV could be transmitted by targeting ACE2, some of the clinical conditions of SARS can be explained consistently. It has actually been confirmed using immunohistochemistry that alveolar epithelium and intestinal epithelium can be infected with SARS-CoV. On the other hand, it has also been confirmed that the cells in which no AEC2 exists can be infected with SARS-CoV, indicating another mechanism for SARS-CoV to enter human cells without targeting AEC2.

Not only damage to human organs caused directly by SARS-CoV but also excessive immune reactions, such as the secretion of too much cytokine, is involved in the patients' conditions of SARS [12]. Excessive immune reaction seems to contribute to the damage to human organs.

5. Clinical Data of SARS for Adults

5.1. Clinical Symptoms and Laboratory Findings

The incubation period ranges from 2 to 10 days, the median being from 4 to 5 days. 14 days is the longest in-

Table 1. Frequency of appearance of clinical symptoms of SARS (%).

Clinical symptoms	Hong Kong Peiris *et al.* [14] (n=50)	Hong Kong Lee *et al.* [15] (n=138)	Singapore Hsu *et al.* [16] (n=20)	Toronto Booth *et al.* [17] (n=144)
Fever	100	100	100	99.3
Shivers	74	73.2	15	27.8
Muscle pain	54	60.9	45	49.3
Cough	62	57.3	75	69.4
Difficulty breathing	20	-	40	41.7
Headache	20	55.8	20	35.4
Dizziness	12	42.8	-	4.2
Phlegm	-	29.0	-	4.9
Diarrhea	10	19.6	25	23.6
Nausea and vomiting	20	19.6	35	19.4
Sore throat	20	23.2	25	12.5
Fatigue	50	-	45	31.2

cubation period that has been reported. After the incubation period, symptoms similar to those of influenza, such as a fever above 38°C, shivers, muscle pain, headache, and fatigue, exhibit themselves. Compared with other viral respiratory infections, the symptoms of inflammation of the upper respiratory tract, such as mucus and sore throat, appear less frequently. 3 to 7 days after the first symptoms are exhibited, symptoms involving the lower respiratory tract appear, such as dry cough and dyspnea. In almost all the cases accompanied by respiratory symptoms, a shadow indicating infiltration of the lungs can be recognized in a chest radiographs and chest CAT scans. Pleural effusion and swelling of the lymph nodes in pulmonary hilum and mediastinum seldom develop. The disease sometimes causes pneumothorax and pneumomediastinum as complications. **Table 1** shows the frequencies of symptoms of the disease [13-17].

In the laboratory findings, a decrease in the number of lymphocytes in peripheral blood can be recognized. The number of lymphocytes decreases gradually immediately after the first symptoms are seen, marks the minimum value in the second week, and recovers again after that. In the lymphocyte subset, all the numbers of CD4, CD8, and B lymphocyte decrease. A slight decrease in platelets, an extension of APTT, a rise in LDH, CPK, and transaminase, and a decline in electrolytes such as Na and K have also been reported. However, these laboratory findings are nonspecific to SARS, so they do not serve to distinguish between SARS and other diseases.

Some reports have indicated that SARS has inapparent infection as well. According to a report by Wilder-Smith et al. [18], there were 6 cases accompanied by inapparent infection, 13%, among 45 carriers of SARS-CoV.

5.2. Progression and Convalescence

Peiris et al. [19] and Wong et al. [20] divide the clinical progression of SARS into three periods. In the first period, the first week, symptoms like those of influenza emerge in connection with active propagation of the virus within the body of the host. In the second period, the second week, the antibody against SARS-CoV starts to be detected in serum, while various symptoms, such as the recurrence of fever after alleviation, diarrhea, and aggravation and shift of the shadow in chest radiographs are observed. Not only damage directly caused by the virus, but also excessive immune reaction is involved in such symptoms. In the third period, the third week, 80% of the patients get better, but the remaining 20% get worse, the symptoms aggravated to ARDS.

The case fatality rate of all the reported cases of SARS has been calculated to be 9.6% [6]. As the main causes of death, severe respiratory failure, multiple organ failure, secondary virus infection, and myocardial infarction are mentioned. The most important factor in connection with unfavorable convalescence is age. WHO shows that the mortality of the patients 24 years old and under is less than 1%, from 25 to 44 years old 6%, from 45 to 64 years old 15%, and 65 years old and over 50% and above. As other significant factors of unfavorable convalescence, diabetes, chronic hepatitis type B, heavy smoking, and chronic obstructive pulmonary disease have been given.

Even in the cases in which the patient recovered from SARS, ground glass opacity remains on many chest CAT scans one month after the onset of illness, and a decline in muscular strength and various degrees of lowering of respiratory functions remain in under 6 to 20% of those after leaving the hospital. Some suffer from post traumatic stress disorder (PTSD) and depression, and some need psychological counseling [21].

As for the antibody titer against the virus, the values for both IgG antibody and neutralizing antibody decrease gradually after they peak at 4 months after the onset of illness, and the positive rate declines to about half in 36 months [22].

6. SARS in Children

6.1. Epidemiology

Children under 18 years old account for only 5% of all the patients reported during the last worldwide epidemic of SARS. The reason why so few children were infected with SARS is unknown.

There seems to be no report of an accurate SARS case fatality rate among children. "Consensus Document on the Epidemiology of Sever Acute Respiratory Syndrome (SARS)" [13], published by WHO, quotes the report in Hong Kong, saying the "case fatality rate of patients from 0 to 24 years old is 0%, but the number of cases itself is also 0." According to Leung et al. [23], no fatalities were reported among 44 children under 18 years old who had been diagnosed as having SARS serologically.

It is thought to be difficult for SARS-CoV to be transmitted to children [13]. Hon et al. [24] reported that 8 children who had been clinically diagnosed as having SARS went to school after the onset of illness; however, they infected none of their classmates. On the other hand, there is another report [25] that an eleven-year-old patient infected four relatives with SARS, which reminds us of the "superspreading event" described below.

There have been no reports of vertical infection from mothers infected with SARS-CoV to their children, nor has SARS-CoV been detected in the umbilical cord blood or amniotic fluid of a mother. According to Shek et al. [26], none of the five infants born to mothers whose infection with SARS-CoV had been confirmed virologically was infected with it by their mothers.

6.2. Clinical Symptoms of SARS in Children

The clinical symptoms of SARS in children are quoted from a paper by Leung et al. [23] which summarizes the cases of 44 patients under 18 years old whose infection with SARS-CoV was confirmed. The frequency of appearance of each symptom is listed as follows: fever, 100%; cough, 63.6%; fatigue, 54.5%; mucus and nasal congestion, 43.2%; phlegm, 36.4%; headache, 36.4%; muscle pain, 36.4%; nausea and vomiting, 29.5%; shivers, 27.3%; diarrhea, 20.5%; sore throat, 13.6%; dizziness, 11.4%; difficulty breathing, 9.1%; stomachache, 9.1%; and anorexia, 9.1%. The youngest case is a 50-day-old baby that had low body temperature, fever, respiratory distress, and cyanosis. When children under 12 years old are compared to those 12 years old and up, the older ones tend to have headache and muscle pain, while younger ones tend to have symptoms similar to those of coryza, e.g., mucus and nasal congestion. Rash, swelling of the lymph nodes, hepatosplenomegaly, and bleeding are not seen in children.

In the laboratory findings, changes similar to those in adults are reported, such as a decrease in leukocyte in peripheral blood, a decrease in lymphocyte, an increase in neutrophil, a decrease in platelets, a rise in ALT, a rise in LDH, and an extension of APTT.

In routine chest radiographs, ground glass opacity and infiltrative shadow of the lung are recognized in many cases, and they can be expanded bilaterally and multiply in some cases.

7. Diagnosis

7.1. Diagnosis with Clinical Case Definition

In the outbreak period in 2003, WHO published the clinical case definition of SARS. According to the definition, a case is considered to be a "suspect case" if the following three criteria are met: (1) fever of 38°C and over, (2) cough and difficulty breathing, and (3) history of exposure to SARS within 10 days before the onset of illness. If the image of pneumonia is confirmed in chest radiographs of "suspect cases," they are considered to be "probable cases." A history of exposure in this context refers to close contact with SARS patients or a history of travel or residence in an epidemic area. However, this clinical case definition cannot be applied in the post-outbreak period because epidemiological information on "epidemic areas" is taken into consideration in this definition. Accordingly, WHO has published "Clinical Case Definition of SARS in Post-Outbreak Period" [27] (**Table 2**). The condition of "SARS Alert" is defined as follows: multiple persons, including health care workers, in the same health care unit fulfilling the above clinical case definition of SARS and with onset of illness within the same 10-day period. Under such circumstances, the appropriate infection control measures should be rapidly implemented, taking possible reemergence of SARS into consideration.

7.2. Pathogenic Diagnosis

There are three methods of pathogenic diagnosis of SARS.

The first method consists of measuring antibody titer against SARS-CoV in serum using ELISA or IFA. This method can be applied in the case of negative antibody tests on acute phase serum followed by positive antibody tests on convalescent phase serum, or a fourfold or greater rise in antibody titer between acute and convalescent phase sera. The antibody starts to be detected around 10 days after the onset of illness, and it is detected at 80 to 100% on the 30th day after the onset of illness. This method is significantly useful for confirmation of the disease but cannot be applied to diagnosis in the early stage.

The second method consists of detecting virus genes using RT-PCR. A positive rate is high in the specimens obtained from the lower respiratory tract and feces.

The third is the method of virus isolation. Every kind of specimen is inoculated into VeroE6 Cells and cultured to observe and identify cytopathic effect. If SARS-CoV can be isolated, diagnosis is determined; however, even if the result proves negative, infection cannot be denied. The cultivation of cells infected with virus necessitates specific technologies and strict safety control, so not every facility can be utilized for this purpose.

Table 2. Case definition of SARS in post-outbreak period by WHO [27].

Clinical case definition of SARS

A person who fulfills all the following conditions:

(1) Fever of 38°C and over;

(2) One or more symptoms of lower respiratory tract illness (cough, difficulty breathing, shortness of breath);

(3) Radiographic evidence of lung infiltrates consistent with pneumonia or RDS, or autopsy findings consistent with the pathology of pneumonia or RDS without an identifiable cause;

(4) No alternative diagnosis can fully explain the illness.

Virological and serological case definition of SARS

A person with symptoms and signs that are clinically suggestive of SARS and with positive laboratory findings for SARS-CoV based on one or more of the following diagnostic criteria:

(a) PCR positive for SARS-CoV PCR positive using a validated method from:

- At least two different clinical specimens (e.g., nasopharyngeal and stool), or
- The same clinical specimen collected on two or more occasions during the course of the illness (e.g., sequential nasopharyngeal aspirates), or
- Two different assays or repeat PCR using a new RNA extract from the original clinical sample on each occasion of testing.

(b) Seroconversion by ELISA or IFA

- Negative antibody test on acute phase serum followed by positive antibody test on convalescent phase serum tested in parallel, or
- Fourfold or greater rise in antibody titer between acute and convalescent phase sera tested in parallel.

(c) Virus isolation

- Isolation in cell culture of SARS-CoV from any specimen, and PCR confirmation using a validated method.

Testing should only be undertaken in a reference laboratory as per WHO recommendations.

Since the end of 2003, rapid diagnosis named Loopamp® using the LAMP method, a nucleic acid amplification method, has been put to practical use in Japan. This method is superior to the conventional PCR method in sensitivity and swiftness but has certain limitations in application to diagnosis in the early stage, as in the case of the PCR method.

8. Route of Infection

8.1. SARS and In-Hospital Infection

Many health care workers were infected with SARS. The risk is especially high when these workers take care of patients without knowing that the patients are infected with SARS-CoV. According to WHO statistics [6], the SARS cases of health care workers account for as high as 21% of all cases worldwide. The percentage of health care workers among all SARS-CoV carriers is highest in Vietnam (57%), Canada (43%), and Singapore (41%). However, this rate becomes lower when SARS becomes prevalent everywhere in the region, as in the case of China. The SARS epidemic often took on a specific pattern of prevalence in which heath care professionals were infected with SARS first, and then it spread to those around them. Many similar cases of in-hospital infection among patients have been reported. Accordingly, prevention of in-hospital infection plays a vital role in the control of SARS.

8.2. Progression After Onset of Illness and Infectivity

SARS-CoV is discharged from respiratory secretions, feces, and the urine of infected persons. Discharge of the virus starts almost at the same time as the onset of illness, but the amount of the virus discharged is thought to be relatively low in the early stage. According to the study by Peiris et al. [14], the positive rate of SARS-CoV in nasopharynx aspirate increases gradually after the onset of illness, reaches its peak at around the 10^{th} day, and decreases gradually until around the third week. The amount of the virus in feces reaches its peak at around the 12^{th} to 14^{th} day after the onset of illness and decreases gradually until around the end of the first month. The amount of discharged virus in the urine follows almost the same pattern as the amount in the feces. Thus, the amount of discharged virus reaches its peak at around the 10^{th} to 12^{th} day after onset of illness, so the infectivity of the virus is estimated to be the highest during this period. In fact, when SARS patients were segregated within the fifth day after onset of illness, secondary infection seldom occurred [13].

SARS-CoV has been reported detected from the respiratory tract and feces even one month and longer after the onset of illness, but there is no clinical report on the secondary infection from patients 10 days or longer after their temperature dropped [13].

8.3. Infection Route

The main infection route of SARS is droplet infection. Therefore, the risk of infection is especially high when exposed to the cough or sneeze of a patient at short distance, and when the suction of sputum, endotracheal intubation, or bronchoscopy are conducted.

The possibility of airborne infection, droplet nuclei infection, cannot be denied. In fact, the existence of SARS-CoV was confirmed in the air of the hospital room of SARS-patients using the RT-PRC method [28]. The Centers for Disease Control and Prevention of the United States, the CDC, notes in its "Guidelines for Isolation Precautions" [29] that SARS-CoV can be transmitted through airborne infection in limited spaces under the specific conditions. The specific conditions in this context refer to

the procedures, such as noninvasive artificial respiration, high-flow oxygen inhalation, and bronchoscopy, in which droplets from the respiratory tract are likely to generate aerosol.

Contagion can also occur. Because a large number of viruses are discharged not only from the respiratory tract but also in feces, as mentioned above, one must pay attention when treating excreta. SARS-CoV remains stable in urine and feces at room temperature for at least in 1 to 2 days, and in diarrhea for as long as 4 days. Furthermore, SARS-CoV has been detected even on plastic or stainless surfaces after 72 hours [13]. Booth et al. [28] showed that PCR-positive samples were obtained on a bed table and on a television remote controller in a patient's room. Accordingly, hygienic treatment of the hands and fingers after treating patients is important for the prevention of the spread of SARS.

8.4. Infectivity

As the index to indicate infectivity, Ro, or basic reproduction number, is used. The index indicates the average number of patients infected secondarily by one patient on condition that no specific measure is taken to prevent infection in a certain population, all the members of which are supposed to be susceptible to infection. The Ro of SARS-CoV is estimated to be 2 to 4. This value is lower than 2 to 5 in HIV, 5 to 10 in smallpox, 5 to 25 in influenza during a pandemic period, and the values of many other infectious respiratory diseases [30].

Regarding the infectivity of SARS in ordinary life, the study by Leung et al. [31] provides useful information. In this study, IgG antibody titer against SARS-CoV was measured for 1,068 individuals who had been in contact with SARS-patients in their ordinary life, and only 2 individuals, or 0.19%, tested positive as a result.

Although the Ro of SARS-CoV is relatively low and its infectivity is not so strong, attention must be paid to the fact that "superspreading events" occasionally occur. This is the phenomenon in which the number of patients infected secondarily by one patient surpasses the average number by far. Superspreading events were observed not only in Singapore and Hong Kong, but also in other countries. However, its mechanism is unknown.

8.5. Infection from Patients Without Symptoms

Inapparent infection of SARS has been confirmed as mentioned above. It was also reported that SARS-CoV was detected from respiratory secretions and feces in 10% of such inapparent infections [13]. Thus, theoretically, the possibility of secondary infection from people with inapparant SARS infections cannot be denied. However, there have been no decisive cases of secondary infections from such patients. In addition, there have been no reports of secondary infections from SARS patients during the incubation period [13]. Thus, it may be concluded that the possibility of infection from SARS patients without symptoms, such as those with inapparent infections or during the incubation period, is extremely low.

9. Measures to Prevent Infection

9.1. Outpatient / Triage [32]

When patients who suspect they may have SARS come to an outpatient clinic, it is necessary to have them wear masks and to separate them physically from other patients. Medical staff wearing goggles and masks such as Particulate Respirator Type N95 mask should guide the patients concerned into the segregation area. Used gloves, stethoscopes, and other medical instruments are to be disposed of or disinfected in the appropriate manner because they could also cause infection.

During medical consultation and treatment, not only for SARS patients but also for others with the acute respiratory disease-like symptoms such as fever and cough, the Cough Etiquette (wearing of masks by patients, wearing of surgical masks by medical staff, etc.) is recommended in addition to standard precautionary measures to reduce the risk of infection.

9.2. Hospitalization [32]

SARS patients, including those suspected of having SARS, are hospitalized in principle in depressurized rooms with doors closed. If a depressurized room is not provided, the patients are hospitalized in single rooms. Multiple SARS patients may be in the same room for cohort isolation. If the patients' rooms are not equipped with exclusive air conditioners, the operation of air conditioning is stopped, and the windows in the room are opened for ventilation. In medical consultation and treatment, "full barrier precautions," including precautionary measures for each infection route, "air (droplet nuclei)," "droplet," and "contact," are implemented in addition to the standard precautionary measures. To be concrete, masks such as Particulate Respirator Type N95, gloves, goggles or similar eye protection, disposable gowns, aprons, and shoes from which contamination can be removed are worn. All the individuals entering the segregated area are obliged to wear such personal protective equipment (PPE). The movement of SARS patients to outside of the segregation area is avoided to the extent possible. However, if such movement is unavoidable, the patients concerned must wear masks. Disposable medical instruments are to be used for SARS patients whenever possible and disposed of in an appropriate manner after their usage. If they are to be reused, they are sterilized or disinfected in the appropriate manner. As disinfectants, alcohol is suitable for living bodies; sodium hypochlorite and glutaraldehyde are suitable for medical instruments.

It is generally important to educate and train all hospital staff in the measures to prevent infection.

10. Medical Treatment and Development of Vaccine

10.1. Symtomatic Treatment

In the early stage of SARS, it is recommended that a suitable antibacterial agent targeting community-acquired

pneumonia be given, because SARS is difficult to distinguish from the pneumonia caused by other microbes. In this case, fluoroquinolone and macrolide are selected targeting atypical pneumonia, which has symptoms similar to those of SARS. If pneumonia is aggravated and respiratory failure is caused as a complication, oxygen therapy and artificial respiration are necessary. In SARS, pneumothorax and pneumomediastinum are caused as complications in 20% of all cases during artificial respiration; thus, attention must be paid to barotrauma.

10.2. Antiviral Agent

Effectiveness against SARS has not been established for any antiviral agents. During the SARS epidemic, ribavirin was used in many cases, but its effectiveness is unknown. In vitro, it has been shown that ribavirin cannot contain the proliferation of SARS-CoV within the range of the concentration of ribavirin, which can be reached clinically.

The effectiveness of lopinavir/ritonavir, a protease inhibitor, has been indicated clinically. In the cases in which this medicament was given against SARS, the number of ARDS as complications and that of death were reported to decease significantly [33].

Furthermore, it has been indicated in the experiments in vitro that nelfinavir, calpain inhibitor VI, calpain inhibitor III, etc. strongly prevent the proliferation of SARS-CoV. Many other medicaments, such as glycyrrhizin, nitric oxide, cathepsin L, and niclosamide as vermicides, have been selected for the fundamental examinations for effectiveness against SARS-CoV. However, their clinical effectiveness has not been confirmed.

10.3. Vaccines

Because the neutralizing antibody caused by infection with SARS-CoV in the blood of patients continues to exist at sufficient levels for at least more than half a year, the prevention of infection by means of vaccine is anticipated.

On the surface of particles of SARS-CoV, spikes which consist of the S (spike) protein protrude. This S protein is thought to be involved in the generation of the neutralizing antibody. A vaccine is being developed applying this process. For example, Buchholz et al. [34] and Bukreyev et al. [35] inoculated experimental animals with the S protein of SARS-CoV using expressed recombinant virus and confirmed a significant rise in neutralizing antibody titer and a containment of the discharge of the viruses. Yang et al. [36], using the DNA vaccine incorporating the genes to code the S protein, and Yokota et al. [37], using the inactivated SARS-CoV vaccine, both succeeded in immunizing mice. Many other fundamental studies on the vaccine have been reported, and many of them have indicated the effectiveness of vaccines.

Nevertheless, some have made cautious comments on the vaccines. Many of these cautious comments have been based on the knowledge obtained from the vaccine development to treat animal coronavirus. For example, the S protein can vary in a short period, so vaccines produced from the same protein cannot alone induce enough protective immunity. There have been some cases in which the use of vaccine could even reinforce the infectivity of the virus. In the case of the live vaccine produced from chicken coronavirus, it has been pointed out that the recombination of the genes could occur between vaccine strains and wild ones, with a new virus possibly emerging.

10.4. Immune Modulator

Because SARS is thought to cause ARDS as a complication due to excessive immune reaction after infection with the virus, immune modulators, especially steroids, were used in many cases during the last pandemic. There is a study [38] that reports the effectiveness of steroids, while others insist steroids should not be used, not only because of their ineffectiveness but also because of their serious side effects. The application of Interferon to medical treatment is now being examined because it can contain the proliferation of SARS-CoV in vitro.

11. Possibility of Resurgence of SARS

As of December 2010, there has been no sign of the resurgence of SARS, but the possibility remains.

In terms of sites that may serve as originating points of SARS resurgence, laboratories may be considered to have the highest probability, as 3 cases of SARS infection within laboratories have already been reported since the official declaration of the end of the SARS epidemic. The first case was in September, 2003 at the Institute of Microbiology of the National University of Singapore, the second was in December of the same year at the Institute of Preventive Medicine of the Taiwan National Defense University, and the third was in April, 2004 at the National Institute of Virology in China.

These cases were caused by the inappropriate treatment of SARS-CoV at the laboratory. It is unknown how many institutes are keeping SARS-CoV. If SARS-CoV is not put under strict biosafety and biosecurity control, the possibility that similar leakages of the virus could lead to a worldwide epidemic cannot be denied.

SARS-CoV could also be transmitted again from animals to humans. As mentioned above, SARS has an aspect of zoonosis. The fact that SARS-CoV has natural hosts in the animal world indicates the possibility the virus could reenter human society from the animal world.

12. Effects of Measures Against Novel Influenzas

During the world-wide epidemic in 2003, WHO issued a recommendation to defer travel to epidemic areas. Various countries tried to prevent the prevalence of the virus by tightening their quarantine systems. In hospitals in Taiwan, Singapore, etc., fever clinics were established to sep-

arate SARS patients, including suspected cases, from others as a precaution against in-hospital infection. Health care workers adopted "full barrier precautions" to protect themselves from the virus. These strategies had significant effects on measures against later emerging infections. The experience gained during the worldwide epidemic of SARS has been applied to the 2005 "WHO Global Influenza Preparedness Plan" [39] and the measures taken against the highly pathogenic avian influenza A/H5N1.

The novel influenza Pandemic H1N1 2009, which originated in Mexico in 2009, has lower pathogenicity than was first expected. Thus, many have criticized the measures taken against the pandemic in 2009 as excessive. However, the author of this paper considers it wise to adopt the strict, even seemingly excessive measures immediately after the emergence of the novel influenza [40]. This opinion is based on the experiences of the author of the survey in Hanoi, Vietnam immediately after the beginning of the epidemic of SARS in 2003. A hospital in Hanoi accepted a pneumonia patient, not knowing this patient had been infected with SARS. As a result, many medical workers were infected by him, and some of them died. The strict measures can be loosened after the characteristics of the pathogen have been clarified to some degree and the prospects for prevention and treatment of the infection have come into sight.

13. Conclusions

Nobody knows whether SARS will reemerge or not, but it is highly possible that similar infections will emerge in the future. Although there has been much suffering, there has also been much learned from SARS. Many indications are included in such experiences to challenge novel infections that may emerge one after another in the future. Much of the experience gained in the epidemic of SARS can be also applied to the treatment of patients infected with avian influenza A/H5N1, on which attention is now focused, and can be applied to measures against other novel influenzas. Preparedness for the reemergence of SARS could lead to precautions against other emerging infections and bioterrorism, as well as to the improvement of biosafety and biosecurity.

References:

[1] K. Y. Yuen et al., "SARS: a historical perspective from Hong Kong. Severe acute respiratory syndrome" (Edited by M. Peiris et al.), pp. 1-12, Blackwell, Massachusetts, USA, 2005.

[2] Centers for Disease Control and Prevention, "Update: outbreak of severe acute respiratory syndrome-worldwide," MMWR Vol.52, No.12, pp. 241-246, 2003.

[3] J. S. Peiris et al., "Coronavirus as a possible cause of severe acute respiratory syndrome," Lancet Vol.361, No.9366, pp. 1319-1325, 2003.

[4] T. G. Ksiazek et al., "A novel coronavirus associated with severe acute respiratory syndrome," N. Engl. J. Med., Vol.348, No.20, pp. 1953-1966, 2003.

[5] C. Drosten et al., "Identification of a novel coronavirus in patients with severe acute respiratory syndrome," N. Engl. J. Med., Vol.348, No.20, pp. 1967-1976, 2003.

[6] World Health Organization, "Cumulative number of reported probable cases of severe acute respiratory syndrome (SARS)," 21 April 2004, http://www.who.int/csr/sars/country/en/index.html

[7] C. C. Vincent et al., "Severe acute respiratory syndrome coronavirus as an agent of emerging and reemerging infection," Clin. Microbiol. Rev., Vol.20, No.4, pp. 660-694, 2007.

[8] S. K. P. Lau et al., "Severe acute respiratory syndrome coronavirus-like virus in Chinese horseshoe bats," PNAS, Vol.102, No.39, pp. 14040-14045, 2005.

[9] W. Li et al., "Bats are natural reservoirs of SARS-like coronaviruses," Science, Vol.310, No.5748, pp. 676-679, 2005.

[10] P. Y. Chong et al., "Analysis of death during the severe acute respiratory syndrome (SARS) epidemic in Singapore. Challenges in determining a SARS diagnosis," Arch. Pathol. Lab. Med., Vol.128, No.2, pp. 195-204, 2004.

[11] W. Li et al., "Angiotensin-converting enzyme 2 is a functional receptor for the SARS coronavirus," Nature, Vol.426, No.6965, pp. 450-454, 2003.

[12] J. Gu and C. Korteweg, "Pathology and pathogenesis of severe acute respiratory syndrome," Am. J. Pathol., Vol.170, No.4, pp. 1136-1147, 2007.

[13] World Health Organization, "Consensus document on the epidemiology of sever acute respiratory syndrome (SARS)," http://www.who.int/csr/sars/en/WHOconsensus.pdf

[14] J. S. M. Peiris et al., "Clinical progression and viral load in a community outbreak of coronavirus-associated SARS pneumonia: a prospective study," Lancet, Vol.361, No.9371, pp. 1767-1772, 2003.

[15] N. Lee et al., "A major outbreak of severe acute respiratory syndrome in Hong Kong," N. Engl. J. Med., Vol.348, No.20, pp. 1986-1994, 2003.

[16] L. Y. Hsu et al., "Severe acute respiratory syndrome (SARS) in Singapore: clinical features of index patient and initial contacts," Emerg. Infec. Dis., Vol.9, No.6, pp. 713-717, 2003.

[17] C. M. Booth et al., "Clinical features and short-term outcomes of 144 patients with SARS in the greater Toronto area," JAMA, Vol.289, No.21, pp. 2801-2809, 2003.

[18] A. Wilder-Smith et al., "Asymptomatic SARS coronavirus infection among healthcare workers, Singapore," Emerging Infectious Diseases, Vol.11, No.7, pp. 1142-1145, 2005.

[19] J. S. M. Peiris et al., "Clinical progression and viral load in a community outbreak of coronavirus-associated SARS pneumonia: a prospective study," Lancet, Vol.361, No.9371, pp. 1767-1772, 2003.

[20] G. W. K. Wong and D. S. C. Hui, "Severe acute respiratory syndrome (SARS): epidemiology, diagnosis and management," Thorax, Vol.58, No.7, pp. 558-560, 2003.

[21] C. M. Tansey et al., "One-year outcomes and health care utilization in survivors of severe acute respiratory syndrome," Arch. Intern. Med., Vol.167, No.12, pp. 1312-1320, 2007.

[22] W. C. Cao et al., "Disappearance of antibodies to SARS-associated coronavirus after recovery," N. Engl. J. Med., Vol.357, No.11, pp. 1162-1163, 2007.

[23] C. Leung et al., "Severe acute respiratory syndrome among children," Pediatrics, Vol.113, No.6, pp. e535-544, 2004.

[24] K. L. E. Hon et al., "Clinical presentations and outcome of severe acute respiratory syndrome in children," Lancet, Vol.361, No.9370, pp. 1701-1703, 2003.

[25] W. Chan et al., "Epidemiological linkage and public health implication of a cluster of severe acute respiratory syndrome in an extended family," Pediatr. Infect. Dis. J., Vol.23, No.12, pp. 1156-1159, 2004.

[26] C. C. Shek et al., "Infant born to mothers with severe acute respiratory syndrome," Pediatrics, Vol.112, No.4, pp. e254-256, 2003.

[27] World Health Organization, "Alert, verification and public health management of SARS in the post – outbreak period," Available at http://www.who.int/csr/sars/postoutbreak/en/

[28] T. F. Booth et al., "Detection of airborne severe acute respiratory syndrome (SARS) coronavirus and environmental contamination in SARS outbreak units," J. Infect. Dis., Vol.191, No.9, pp. 1472-1477, 2005.

[29] Centers for Disease Control and Prevention, "Guideline for isolation precautions: preventing transmission of infectious agents in healthcare settings 2007," http://www.cdc.gov/ncidod/dhqp/pdf/guidelines/Isolation2007.pdf

[30] R. M. Anderson et al., "Epidemiology, transmission dynamics, and control of SARS: the 2002-2003 epidemic. SARS a case study in emerging infections," (Edited by A. R. McLean), pp. 61-80, Oxford University Press, Oxford, 2005.

[31] G. M. Leung, P. H. Chung, T. Tsang et al., "SARS-CoV antibody prevalence in all Hong Kong patient contacts," Emerg. Infect. Dis., Vol.10, No.9, pp. 1653-1656, 2004.

[32] World Health Organization, "Hospital infection control guidance for severe acute respiratory syndrome (SARS)," revised 24 April 2003. Available at http://www.who.int/csr/sars/infectioncontrol/en/

[33] C. M. Chu et al., "Role of lopinavir/ritonavir in the treatment of SARS: initial virological and clinical findings," Thorax, Vol.59, No.3, pp. 252-256, 2004.
[34] U. J. Buchholtz et al., "Contributions of the structural proteins of severe acute respiratory syndrome coronavirus to protective immunity," Proc. Natl. Acad. Sci. USA, Vol.101, No.26, pp. 9804-9809, 2004.
[35] A. Bukreyev et al., "Mucosal immunization of African green monkeys (Cercopithecus aethiops) with an attenuated parainfluenza virus expression the SARS coronavirus spike protein for the prevention of SARS," Lancet, Vol.363, No.9427, pp. 2122-2127, 2004.
[36] Z. Yang et al., "A DNA vaccine induces SARS coronavirus neutralization and protective immunity in mice," Nature, Vol.428, No.6982, pp. 561-564, 2004.
[37] Y. T. Yokota et al., "Formalin-treated UV inactivated SARS coronavirus vaccine retains its immunogenicity and promotes Th2-type immune responses," Jpn. J. Infect. Dis., Vol.60, Nos.2-3, pp. 106-112, 2007.
[38] R. C. Chen et al., "Treatment of severe acute respiratory syndrome with glucosteroids, the Guangzhou experience," Chest, Vol.129, No.6, pp. 1441-1452, 2006.
[39] World Health Organization, "WHO global influenza preparedness plan. The role of WHO and recommendations for national measures before and during pandemics," World Health Organization, 2005.
[40] A. Kawana, K. Teruya, N. Yamashita, "SARS; Severe Acute Respiratory Syndrome," The Journal of the Japanese Association for Infectious Diseases, Vol.77, pp. 303-309, 2003 (in Japanese).

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2009年新型インフルエンザパンデミックにおける重症化症例の実態―特に肺炎について

川名明彦

キーワード●新型インフルエンザ（A/H1N1），パンデミック，重症，肺炎

はじめに

2009年春，世界的な流行となったパンデミック（H1N1）2009ウイルス感染症［以下，新型インフルエンザ(A/H1N1)］は，スペインかぜなど過去のパンデミックに比較すると，重症化率や死亡者数の観点からは被害は軽度だったとされる．しかし，いわゆる季節性インフルエンザとは異なる特徴も指摘されており，また比較的まれではあるが，健常青壮年における死亡例の報告があるなど注目すべき点がある．

Ⅰ 新型インフルエンザ(A/H1N1)の疫学

1. 世界の状況

WHO（世界保健機関）は，新型インフルエンザ（A/H1N1）の統計について2009年11月の時点で次のように報告している[1]．

人口10万人当たりの入院患者数は，日本：2.9，アメリカ：3.0，カナダ：5.8，メキシコ：9.3，チリ：10.8，オーストラリア：22.5，ニュージーランド：23.3，アルゼンチン：24.5等であった．致死率についてはおおむね0.5%未満と考えられ，人口100万人当たりの死亡者数で表すと，日本：0.2，イギリス：2.2，カナダ：2.8，メキシコ：2.9，アメリカ：3.3，ニュージーランド：4.4，チリ：8.1，オーストラリア：8.6，アルゼンチン：14.6等となる．これらの数値は，国によって集計方法が異なるため単純比較はできない．

新型インフルエンザ(A/H1N1)の疫学的特徴[2]として，小児と若年成人の患者数が多いが，年齢階級別死亡率は50～60歳代が高いことが挙げられる．重症化のリスク要因は，慢性肺疾患，喘息，糖尿病等の基礎疾患や妊娠，肥満とされる．

2. 日本の状況

厚生労働省の報告[3]によると，2010年第11週（3月21日）の時点で，日本全国の医療機関を受診した新型インフルエンザ(A/H1N1)の累積推計患者数は約2,068万人（日本の総人口の約16%）である．0～19歳が7割以上を占める．

新型インフルエンザ（A/H1N1）により1万7,640人（累積推計患者数の0.09%）が入院を要したが，中高年，特に70歳以上の年齢で入院率が高かった．入院患者37%に基礎疾患があり，その内訳は，慢性呼吸器疾患，慢性心疾患，糖尿病などであった．

入院を要した例のうち，重症化した割合を年齢階級ごとに示したのが図1である[3,4]．重症とは，ICU入室，人工呼吸器装着，急性脳症のいずれかに該当するものと定義されている．ICU入室率，人工呼吸器装着率はおおむね高齢者で高いが，季節性インフルエンザでは重症化することがまれな40～50歳代が最も高い点は注目される．

Characteristics of Severe Cases of Pandemic (H1N1) 2009 Influenza
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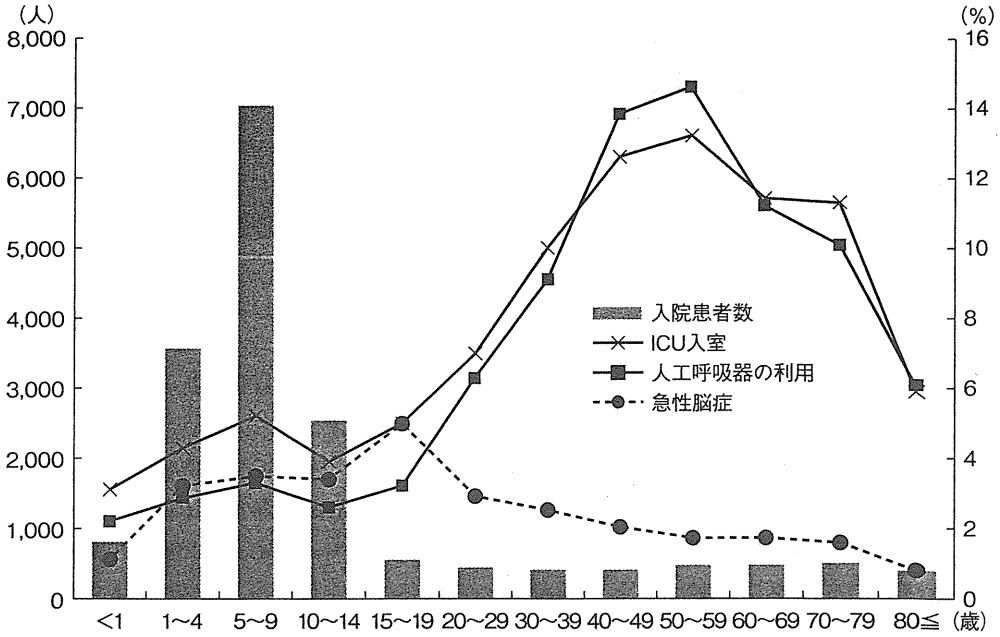

図1　年齢階級別入院患者数と重症例の割合
(3月23日までの累積入院患者1万7,640人)

[厚生労働省新型インフルエンザ対策推進本部:今般の新型インフルエンザ(A/H1N1)対策について—対策の総括のために. 平成22年3月31日. 厚生労働省新型インフルエンザ(A/H1N1)対策総括会議資料1;12より作成]

わが国では2010年3月23日までに新型インフルエンザ(A/H1N1)による死亡者は198人と報告され，累積推計受診者数を分母として概算すると，その致死率は0.001%以下となる．

II 新型インフルエンザ(A/H1N1)の臨床像と重症化

1. 一般にみられる症状[2]

大多数の新型インフルエンザ(A/H1N1)は比較的軽症で予後も良好である．

潜伏期間は約1.5～3日で，これは季節性インフルエンザとほぼ同様である．

症状は，上気道炎程度の例も多く，発熱を伴わない例も8～32%程度あるとされる．それ以外の大部分は典型的な「インフルエンザ様症状」を呈する．隔離の目的で入院した426人について検証した中国の報告[5]によると，38.1℃以上の発熱が36%，咳嗽69.5%，咽頭痛36.6%，喀痰24.5%，鼻汁23.7%，頭痛19.5%，鼻閉16%，倦怠感10.3%，筋肉痛・関節痛10.1%，悪寒7.5%，下痢2.8%，嘔気・嘔吐1.9%等となっている．

2. 重症化とその内訳

Jainら[6]は，アメリカで新型インフルエンザ(A/H1N1)のために入院した272人を対象に検討したところ，40%に肺炎を認めた．入院患者の75%に抗インフルエンザウイルス薬が投与されたが，発症後投与開始までの期間の中央値は3日であった．入院患者の25%はICUに入室した．ICUに入室した患者の63%は人工呼吸管理を要し，36%は急性呼吸窮迫症候群(ARDS)，31%は敗血症と臨床診断された．入院患者の7%が死亡した．死亡した患者の90%には抗インフルエンザウイルス薬が使用されたが，発症後投与開始までの期間の中央値は8日で，48時間以内に開始されていた者はいなかった．抗インフルエンザウイルス薬投与の遅れと予後不良との関連が推察できる．

オーストラリア・ニュージーランドの研究グループ[7]は，新型インフルエンザ（A/H1N1）でICUに入室した患者722人を対象に検討した．それによると64.6%は人工呼吸管理を必要とした．48.8%はARDSあるいはウイルス性肺炎，20.3%は細菌性肺炎と診断され，14.3%が死亡した．予後不良と関連する因子として，ICU入室時に侵襲的人工呼吸が必要であること，何らかの合併症があること，高齢であることが挙げられた．

3. 重症呼吸器合併症の臨床像

Gómez-Gómezら[8]は，メキシコでみられたインフルエンザ肺炎50例（平均年齢38.4歳）を検討した．36%はICU管理を要し，20%が死亡したが，基礎疾患のない若年者にも重症肺炎がみられた．画像上，全症例に単一葉～複数葉の浸潤影（consolidation）を，42%に間質性陰影を，6%に胸水を認めた．

CTでは，多発性のすりガラス陰影や肺胞性浸潤影と気管支透亮像など多彩であるとの報告が多い[2]．

細菌性肺炎の合併は20～30%にみられたとするものが多い．新型インフルエンザ(A/H1N1)で死亡した77人（年齢中央値31歳）の剖検肺を用いたアメリカの検討[9]では，22人(29%)において細菌感染の証拠が認められ，その内訳は*S. pneumoniae*，*S. aureus*，*S. pyogenes*，*S. mitis*，*Haemophilus influenzae*の順であった．

III 重症肺炎の病態

1. 病態に関する知見

ウイルスのヘマグルチニンと宿主レセプターの結合に関する研究[10,11]によると，新型インフルエンザ(A/H1N1)ウイルスは宿主の上気道～気管に存在するSAα2,6 Galレセプターのほかに，末梢気道，肺胞上皮細胞に存在するSAα2,3 Galレセプターにも結合する．肺胞上皮細胞へのウイルス感染はガス交換を障害し，呼吸不全の病態を説明しうる．

van den Brandら[12]はフェレットを用いて感染実験を行い，ウイルスの呼吸器系における局在を調べている．鳥インフルエンザ(A/H5N1)ウイルスは肺胞に多くみられたのに対し，新型インフルエンザ(A/H1N1)ウイルスは気管支，細気管支，肺胞のいずれにもみられた．

Bermejo-Martinら[13]は，重症の新型インフルエンザ(A/H1N1)患者では血中のIL-15，IL-12 p70，IL-8，IL-6が優位に増加しており，これらが重症化のマーカーとなりうると報告した．また，死亡例やARDS例では各種サイトカインが増加しているという報告[14]がある．このようなメディエータの産生亢進が，過剰な炎症反応を惹起し，血管透過性の亢進や肺間質の浮腫をもたらし，呼吸不全を招来することが想像される．

2. 重症肺炎の病理

新型インフルエンザ(A/H1N1)ウイルスの感染により死亡した症例の肺組織において，種々の程度のびまん性肺胞障害（diffuse alveolar damage），肺硝子膜形成，肺胞隔壁の肥厚像，気管気管支炎，および壊死性細気管支炎が観察されている．また，血球貪食像や血栓も指摘されている[2,8,15]．そのほか，比較的早期の所見として肺血管のうっ血，肺胞出血もみられる．これらの変化に加え，細菌感染の合併がみられることも多く，病態を複雑にしている．

おわりに

新型インフルエンザ(A/H1N1)の大部分は軽症で予後良好といえる．しかし，基礎疾患のない若年者，青壮年層においてまれではあるが重症化が報告されている．その大部分は肺炎を合併している．ウイルス感染に対する過剰なサイトカイン反応や，肺胞や末梢気道へのウイルス感染に加え，二次性の細菌感染等が加わり複雑な病態が生じていると考えられる．本ウイルス感染症の重症化の病態解明は，今後の新型インフルエンザ対策に貢献すると思われる．

文　献

1) Transmission dynamics and impact of pandemic influenza A (H1N1) 2009 virus. *Wkly Epidemiol Rec* 2009 ; 84 : 481–484.
2) Writing Committee of the WHO Consultation on Clinical Aspects of Pandemic (H1N1) 2009 Influenza, Bautista E, Chotpitayasunondh T, *et al* : Clinical aspects of pandemic 2009 influenza A (H1N1) virus infection. *N Engl J Med* 2010 ; 362 : 1708–1719.
3) 厚生労働省新型インフルエンザ対策推進本部：今般の新型インフルエンザ（A/H1N1）対策について―対策の総括のために．平成22年3月31日．厚生労働省新型インフルエンザ（A/H1N1）対策総括会議資料 1. http://www.mhlw.go.jp/bunya/kenkou/kekkaku-kansenshou04/dl/infu100331-02.pdf
4) Wada K, Nishiura H, Kawana A : An epidemiological analysis of severe cases of the influenza A (H1N1) 2009 virus infection in Japan. *Influenza Other Respi Viruses* 2010 ; 4 : 179–186.
5) Cao B, Li XW, Mao Y, *et al* : Clinical features of the initial cases of 2009 pandemic influenza A (H1N1) virus infection in China. *N Engl J Med* 2009 ; 361 : 2507–2517.
6) Jain S, Kamimoto L, Bramley AM, *et al* : Hospitalized patients with 2009 H1N1 influenza in the United States, April-June 2009. *N Engl J Med* 2009 ; 361 : 1935–1944.
7) ANZIC Influenza Investigators, Webb SA, Pettilä V, *et al* : Critical care services and 2009 H1N1 influenza in Australia and New Zealand. *N Engl J Med* 2009 ; 361 : 1925–1934.
8) Gómez-Gómez A, Magaña-Aquino M, Garcia-Sepúlveda C, *et al* : Severe pneumonia associated with pandemic (H1N1) 2009 outbreak, San Luis Potosí, Mexico. *Emerg Infect Dis* 2010 ; 16 : 27–34.
9) Centers for Disease Control and Prevention (CDC) : Bacterial coinfections in lung tissue specimens from fatal cases of 2009 pandemic influenza A (H1N1) — United States, May-August 2009. *MMWR Morb Mortal Wkly Rep* 2009 ; 58 : 1071–1074.
10) Itoh Y, Shinya K, Kiso M, *et al* : In vitro and in vivo characterization of new swine-origin H1N1 influenza viruses. *Nature* 2009 ; 460 : 1021–1025.
11) Childs RA, Palma AS, Wharton S, *et al* : Receptor-binding specificity of pandemic influenza A (H1N1) 2009 virus determined by carbohydrate microarray. *Nat Biotechnol* 2009 ; 27 : 797–799.
12) van den Brand JM, Stittelaar KJ, van Amerongen G, *et al* : Severity of pneumonia due to new H1N1 influenza virus in ferrets is intermediate between that due to seasonal H1N1 virus and highly pathogenic avian influenza H5N1 virus. *J Infect Dis* 2010 ; 201 : 993–999.
13) Bermejo-Martin JF, Ortiz de Lejarazu R, Pumarola T, *et al* : Th1 and Th17 hypercytokinemia as early host response signature in severe pandemic influenza. *Crit Care* 2009 ; 13 : R201.
14) To KK, Hung IF, Li IW, *et al* : Delayed clearance of viral load and marked cytokine activation in severe cases of pandemic H1N1 2009 influenza virus infection. *Clin Infect Dis* 2010 ; 50 : 850–859.
15) Mauad T, Hajjar LA, Callegari GD, *et al* : Lung pathology in fatal novel human influenza A (H1N1) infection. *Am J Respir Crit Care Med* 2010 ; 181 : 72–79.

DOI:10.1111/j.1750-2659.2010.00143.x
www.influenzajournal.com

Original Article

An epidemiological analysis of severe cases of the influenza A (H1N1) 2009 virus infection in Japan

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Accepted 29 April 2010. Published online 15 June 2010.

Background The age distribution of confirmed cases with influenza A (H1N1) 2009 has shifted toward children and young adults, in contrast to interpandemic influenza, because of the age specificities in immunological reactions and transmission characteristics.

Objectives Descriptive epidemiological analysis of severe cases in Japan was carried out to characterize the pandemic's impact and clinical features.

Methods First, demographic characteristics of hospitalized cases (n = 12 923), severe cases (n = 894) and fatal cases (n = 116) were examined. Second, individual records of the first 120 severe cases, including 23 deaths, were analyzed to examine potential associations of influenza death with demographic variables, medical treatment and underlying conditions. Among severe cases, we compared proportions of specific characteristics of survivors with those of fatal cases to identify predictors of death.

Results Age distribution of hospitalized cases shifted toward those aged <20 years; this was also the case for deaths without underlying medical conditions. Deaths in adults were mainly seen among those with underlying medical conditions, resulting in an increased risk of death as a function of age. According to individual records, the time from onset to death in Japan appeared rather short compared with that in other countries.

Conclusion The age specificity of severe cases and their underlying medical conditions were consistent with other countries. To identify predictors of death in influenza A (H1N1) 2009 patients, more detailed clinical characteristics need to be examined according to different age groups and types of manifestations, which should ideally include mild cases as subjects.

Keywords Critical illness, encephalitis, H1N1, influenza, pandemic, respiratory failure.

Please cite this paper as: Wada *et al.* (2010). An epidemiological analysis of severe cases of the influenza A (H1N1) 2009 virus infection in Japan. Influenza and Other Respiratory Viruses 4(4), 179–186.

Introduction

Japan identified its first case of influenza A (H1N1) 2009 virus infection on 9 May 2009, and its incidence has increased steadily until it hit the first peak in November 2009.[1] The unique antigenic features of the virus, the age specificity of transmission (e.g., age-specific contact frequency) and age-dependent immune reactions are thought to have resulted in a high incidence among young adults – an epidemiological profile that is different from interpandemic influenza.[2–8] These characteristics led to a surge in pediatric patients. Severe cases have also been seen among adults, especially among those with underlying medical conditions.[9,10]

To minimize the potential number of deaths attributed to this disease, it is critically important to clarify the epidemiological and clinical features of severe cases, both at individual and at population levels. The purpose of this study is to summarize the epidemiological characteristics of severe cases of influenza A (H1N1) 2009 in Japan, measuring the pandemic impact and describing the clinical features.

Methods

Data and case definition

Our study was composed of two parts. First, we presented epidemiological characteristics of severe cases using the most recent summary statistics (as of 15 December 2009). Second, individual records by 6 October 2009 were analyzed in detail. Hereafter, cases in three different classifications of severity – hospitalized cases, severe cases and critically ill cases – were analyzed. All of these cases were mandatorily reported to the Ministry of Health, Labour

and Welfare (MHLW) of Japan, through local public health offices.

We conducted the following analysis to comply with the research demands of the MHLW. Hospitalized cases refer to those who were admitted to hospital as a result of influenza A (H1N1) 2009 virus infection including confirmed cases (i.e., diagnosed by means of RT-PCR) and probable cases (i.e., those with influenza-like illness who tested positive for influenza A by means of rapid diagnostic testing or with an epidemiological link to a probable or a confirmed case). Until 19 June 2009, all suspected cases had been advised to be admitted to, and monitored at, hospital; thereafter, the Japanese government ceased its isolation policy targeting all cases (i.e. switching their control policy from containment to mitigation). The surveillance of hospital admissions started from 24 July 2009 and thus does not include apparently mild cases, who tended to be admitted during the very early stage of the 2009 pandemic.

Severe cases were defined as confirmed or probable cases who met one of the following conditions: patients who (i) were diagnosed with influenza-associated encephalopathy; (ii) were admitted to an intensive care unit (ICU); (iii) were intubated; or (iv) died. Among these, influenza-associated encephalopathy was defined as those showing clinical symptoms or signs suggestive of acute encephalopathy. These signs and symptoms included altered consciousness (e.g., delirium, confusion and cognitive impairment) and loss of consciousness (e.g., deep coma, coma, semicoma, stupor and somnolence) persisting for longer than 24 h. Cases with meningitis, myelitis and febrile convulsions, without prolonged unconsciousness, were excluded from the influenza-associated encephalopathy. Critically ill cases referred to severe cases excluding influenza-associated encephalopathy. Consequently, critically ill cases represent a portion of severe cases; we used these two definitions of cases with some overlaps, because influenza-associated encephalopathy might potentially be milder than other severe cases. All the severe cases included in our second part of analysis (i.e., analysis of individual records) were confirmed by means of RT-PCR, except for three fatal probable cases (which had positive results from rapid diagnostic testing).

Statistical analysis

First, the summary statistics of the above-mentioned classifications of cases, reported by 15 December 2009, were analyzed. Descriptive epidemiological features of hospitalized cases, severe cases and deaths were summarized – especially age specificity. It should be noted that deaths were mostly included among severe cases (except for those who had not been diagnosed prior to their deaths), and the severe cases were included among hospitalized cases; we analyzed the multiple layers of cases to estimate the age-specific risk of fatal outcome and severe manifestations among severe and hospitalized cases, respectively. Because the age distribution of ICU admissions was not consistently stratified by age group, severe cases in the first part of analysis included those who were intubated and/or diagnosed as influenza-associated encephalopathy. Because the original data obtained from the MHLW were given as summary statistics in discrete age groups, we compared age distributions between different groups by the chi-square test. To measure the impact of the pandemic in Japan and to explore the potential role of age in determining its clinical course, we examined age-specific ratio of deaths to hospitalizations (here, we used the term 'ratio' rather than 'proportion,' because not all fatal cases were reported as hospitalized cases prior to their death event). The ratios of those intubated to hospitalizations and cases of influenza-associated encephalopathy to hospitalizations were also examined by age group. Subsequently, age-specific hospitalization and death rates per population were also examined to estimate the impact of the pandemic at the population level.

Second, to summarize clinical characteristics of severe and critically ill cases, we analyzed individual records of a total of 120 severe cases, including 23 deaths, of patients who developed the disease by 6 October 2009. We investigated potential associations of influenza death with the following variables, seeking potential predictors of death among severe cases: age, gender, time from onset to admission, antiviral treatment, ICU admission, intubation and specific underlying conditions. The times of illness onset, first antiviral treatment and hospital admission were reported as daily data (i.e., only the dates of these events were known); we calculated the time intervals between two events as difference between the two dates plus 1. These demographic and clinical characteristics were analyzed by stratifying severe cases into four sub-categories: (i) those aged <18 years with influenza-associated encephalopathy, (ii) other patients aged <18 years, (iii) patients aged from 18 to 64 years, and (iv) patients 65 years and older. The time from onset to hospitalization was modeled as a continuous variable, while all the remaining variables were dealt as dichotomous variables. We used three cutoff values for antiviral treatment: 1, 2 and 3 days between onset of illness until antiviral treatment was started. When we examined the influence of time from onset to hospitalization on the risk of death, we compared the distribution between those who survived and those who died by means of the non-parametric Wilcoxon test. For the remaining hypothesis testing, Fisher's exact test (two-sided) was employed, comparing the proportion of those with a specific dichotomous factor between those survived and died. The level of statistical significance was set at $P = 0{\cdot}05$.

Results

Pandemic impact in Japan

Figure 1(A–C) shows the age distributions of the cumulative numbers of hospitalized, severe and fatal cases. As of 15 December 2009, 12 923 hospitalizations were reported, among which 508 cases were intubated owing to respiratory failure and 386 cases were diagnosed as influenza-associated encephalopathy. Hospitalized cases were most frequently seen among those aged <20 years; the mean [standard deviation (SD)] and median ages were 12·9 (16·8) and 7·5 years, respectively. Men accounted for 63·7% (n = 8229) of the total. Of the 12923 hospitalized cases, 4567 (35·3%) were reported as having at least one underlying condition. Four major underlying conditions were frequently reported; i.e., chronic cardiovascular disease (n = 234, 1·8%), chronic renal disease (n = 174, 1·3%), chronic respiratory disease (n = 2961, 22·9%) and diabetes (n = 206, 1·6%). Only 41 cases (0·3%) were pregnant women. Mean (SD) and median ages of intubated cases were 23·8 (24·8) and 7·5 years, respectively, while those of influenza-associated encephalopathy cases were 10·0 (9·9) and 7·5 years, respectively. The intubated cases appeared to be significantly older than those with influenza-associated encephalopathy (P < 0·01).

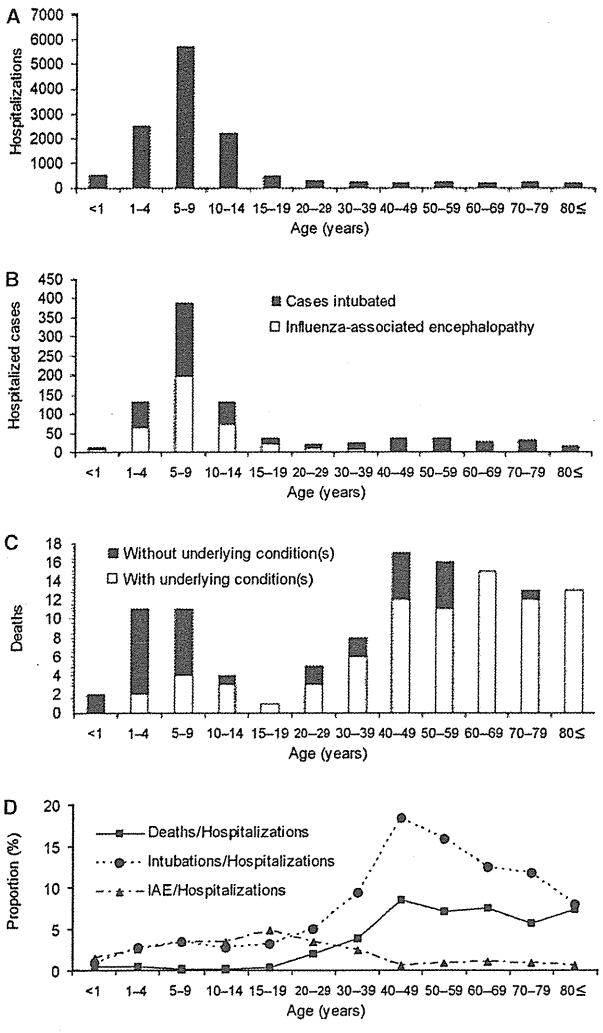

Figure 1. Age distribution of hospitalized cases, severe cases and deaths with influenza A (H1N1) 2009 virus infection in Japan. Panels A–C show the cumulative numbers as of 15 December 2009. (A) Hospitalizations (n = 12 923). (B) Cases intubated (n = 508) or with influenza-associated encephalopathy (n = 386). (C) Deaths stratified by those with (n = 82) and without (n = 34) underlying condition. (D) Age-specific proportions of intubated cases, cases with influenza-associated encephalopathy and deaths among hospitalized cases. IAE, Influenza-associated encephalopathy.

As of 15 December 2009, 116 deaths have been reported. The ratio of deaths to hospitalizations for the entire sample population was 0·89% (i.e., 1:112). Unlike hospitalized and severe cases, the age distribution of fatal cases revealed two peaks, one among children aged <10 years and another among adults aged 40–49 years (Figure 1C). The mean (SD) and median ages were 45·5 (27·5) and 45·0 years, respectively. Men accounted for 59·5% (n = 69). Figure 1(C) stratifies fatal cases by presence or absence of any one underlying condition. Whereas the mean (SD) and median ages of fatal cases without underlying conditions were 23·0 (22·8) and 7·5 years, respectively, the mean (SD) and median ages of fatal cases with at least one underlying condition were 54·9 (23·7) and 55·0 years, respectively. Fatal cases with at least one underlying condition were significantly older than those with no underlying condition (P < 0·01). It is worth noting that 40 out of a total of 41 deaths for those aged 60 years and older had at least one underlying medical condition.

Figure 1(D) shows the ratios of deaths to hospitalizations, intubated cases to hospitalizations and influenza-associated encephalopathy cases to hospitalizations as a function of age. The proportions of intubated cases and influenza-associated encephalopathy cases among the total of hospitalized cases were 3·9% and 3·0%, respectively. The age-specific proportions of intubated patients and deaths among hospitalized cases tend to increase as a function of age, with a peak around those aged 40–49 years. The proportion of influenza-associated encephalopathy cases among hospitalized cases peaked in those aged 15–19 years, with decreasing frequency in older age groups.

Figure 2 shows the age-specific hospitalization rate and mortality rate per population. For the entire Japanese population, the hospitalization rate was estimated at 10·1 per 100 000 population. Similarly, the mortality rate was estimated at 0·1 per 100 000 population. The risk of hospitalizations at the population level was highest among those

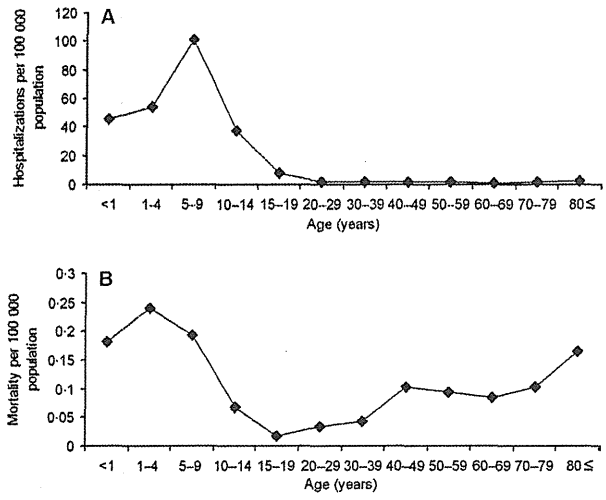

Figure 2. Age-specific hospitalization rate and death rate with influenza A (H1N1) 2009 virus infection in Japan. (A) Age-specific hospitalization rate per 100 000 population. (B) Age-specific mortality rate per 100 000 population. These figures used cumulative numbers of hospitalizations and deaths as of 15 December 2009; estimates throughout the entire course of the pandemic wave are therefore expected to be larger. It should also be noted that those cumulative numbers represent only diagnosed cases and substantial number of undiagnosed cases are not included.

aged 5–9 years (Figure 2A), reflecting the highest number of hospitalized cases in Figure 1(A). Although the age-specific patterns of mortality rate also reflected that of the absolute numbers of deaths in Figure 1(C), children aged from 1 to 4 years yielded the highest mortality estimate (0·24 per 100 000). Especially, it should be noted that pediatric mortality rate among those aged below 10 years appeared to be higher than that among elderly (Figure 2B).

Analysis of first 120 severe cases

Table 1 summarizes demographic and clinical characteristics for the four sub-categories of severe cases. Of the first 120 severe cases whose individual records were available, those aged <18 years accounted for 71·7%. All 11 cases aged 65 years and older resulted in death, while the proportion of deaths among cases aged <18 years and those from 18 to 64 years was smaller (5·3% and 34·8%, respectively). The median age of fatal cases was 57 years and included 13 men and 10 women (Table 2). Men accounted for 63·3% (n = 76) of the total severe cases and 56·5% (n = 13) of total deaths; there was no gender specificity in the risk of death among severe cases (P = 0·53; Table 1).

Of the 120 severe cases, 57 (47·5%) had at least one underlying medical condition (Table 3). Of the 86 cases aged <18 years, 27 (31·4%) had one or more comorbidity, with asthma being the most common (22·9%). Similarly, of the 34 cases aged 18 years or older, 30 (88·2%) had comorbidities, and chronic respiratory disease (23·5%) was the most common. We did not find any underlying conditions that would significantly predict death among the severe or critically ill cases. Pregnant women were not seen in the first 120 severe cases.

The mean (SD) and median times from onset to hospitalization among severe cases were 2·6 (1·7) and 2·0 days, respectively (Table 1). The mean (SD) and median times from onset to death for the 23 fatal cases were 6·7 (4·9) and 5·0 days, respectively.

The timing of antiviral administration did not appear to significantly affect the clinical course (i.e., the risk of death) among either those with influenza-associated encephalopathy or critically ill cases (P > 0·05 for all groups; Table 1). Among the cases with influenza-associated encephalopathy (n = 48), 11 received treatment with zanamivir alone, 8 with zanamivir and oseltamivir, 28 with oseltamivir alone and 1 with no antiviral medication. Unfortunately, the route of administration and the time delay from illness onset to medication were not consistently recorded. There was no fatality among those who received treatment with zanamivir, and the only one case among 11 using zanamivir alone had asthma as the underlying medical condition (the remaining 10 cases did not have specific underlying conditions). Among critically ill cases aged <18 years (n = 38), two received treatment with zanamivir alone, four with a combination of zanamivir and oseltamivir, 30 cases with oseltamivir alone and two with no antiviral medication. The one fatality in this category was seen in a patient with asthma without antiviral treatment whose RT-PCR positive result was only noticed 12 days after onset of illness. All the critically ill cases aged 18 years and older received treatment with oseltamivir except four individuals without medication. The four cases without medication resulted in death. Three fatal cases with influenza-associated encephalopathy were admitted to ICU and intubated. Of 11 deaths among elderly, 8 (72·7%) received antiviral treatment within 3 days of illness onset (Table 1). The major causes of death for the eight deaths included exacerbation of underlying disease (n = 2), acute respiratory distress syndrome (n = 2) and pneumonia (n = 2).

Discussion

This study analyzed severe cases of influenza A (H1N1) 2009 reported to the MHLW of Japan, reviewing the demographic characteristics of cases by examining summary statistics of the national surveillance data and exploring the risk of death among first 120 severe cases whose individual records were available. Whereas the age distribution of hospitalized cases shifted toward those aged <20 years, the distribution of deaths showed two distinct peaks, one among children <10 years of age and another

Table 1. Demographic and clinical characteristics of severe cases with confirmed or probable diagnoses of influenza A (H1N1) 2009 virus infection in Japan

Characteristic	Aged <18 years with influenza-associated encephalopathy *n* = 48 (with 3 deaths) Total (deaths)	Other cases aged <18 years* *n* = 38 (with 1 death) Total (deaths)	Those aged 18–64 years *n* = 23 (with 8 deaths) Total (deaths)	Those aged 65 years and older *n* = 11 (with 11 deaths) Total (deaths)
Gender				
Female	17 (0)	11 (0)	10 (4)	6 (6)
Mean time from onset to hospitalization (days)	2·4 (2·0)	2·4 (2·0)	3·6 (3·3)	3·2 (3·2)
Onset to death (days)				
Mean	(6·0)	(16·0)	(6·3)	(5·4)
Median	(5·0)	(16·0)	(4·5)	(4·0)
Antiviral treatment†				
≤1 day	12 (0)	8 (0)	4 (0)	5 (5)
≤2 days	34 (3)	26 (0)	8 (1)	7 (7)
≤3 days	42 (3)	32 (0)	9 (2)	8 (8)
Admission to intensive care unit (ICU)‡	11 (3)	29 (1)	17 (5)	2 (2)
Intubation	8 (3)	31 (1)	15 (4)	3 (3)

*Cases aged below 18 years reported as severe for reasons other than influenza-associated encephalopathy.
†Time from illness onset to antiviral treatment.
‡Admitted to an intensive care unit at least once during the course of disease. It should be noted that ICU admission and intubation were the criteria to be reported as severe cases.

among those aged 40–49 years. As a consequence, the proportion of deaths among hospitalized cases increased with age, an epidemiological pattern that is consistent with the age-specific case fatality ratio among confirmed cases.[11,12] As an important underlying mechanism of the increased risk of death with age among hospitalized cases, those who died with underlying medical conditions tended to be significantly older than those without. The age-specific mortality rate was highest among those aged <10 years.

Reviewing the findings from the summary statistics, we observed the following:(i) hospitalized cases were mainly seen among children and young adults, which might reflect age-specific immunity to the novel influenza A (H1N1) virus and age-dependent transmission characteristics[2–8]; (ii) a similar age specificity was also seen in deaths among those without underlying medical conditions; and (iii) adult deaths among hospitalized cases, especially in the elderly, were seen among those with underlying medical conditions. The proportion of pregnant hospitalized cases, whose risk of death is believed to be high,[13,14] was rather small in Japan; the underlying mechanism of this phenomenon, e.g., potential influence of the membership structure in households and early treatment of pregnant cases, should be explored in the future.

From the analysis of individual records, four important conclusions can be drawn. First, cases among those aged below 18 years were more frequently reported to be severe than cases in adults, a finding that is specifically different from interpandemic influenza. As more than half of the critically ill cases in the United States, Australia and New Zealand have been adults, our finding may be specific for the Japanese setting.[10,15] It is likely that this finding is partly associated with the definition of severe cases in this study, because a substantial number of influenza-associated encephalopathy cases are included among those aged <18 years. As the epidemic progresses furthermore, the age composition of severe cases may change. Second, the clinical course of this disease appears to have been rapid after onset.[16–19] In particular, the time from onset to death in Japan was rather short compared with those reported elsewhere,[17,18,20] indicating a critical need to start appropriate medical management shortly after illness onset. Third, approximately half of the cases were accompanied by at least one underlying condition; this proportion was particularly high among adults. The observed proportion of severe cases with at least one underlying condition was smaller among children compared with other countries, but the estimate among adults was consistent with the United States and Canada,[15,16] perhaps reflecting higher frequency of diagnosis for influenza-associated encephalopathy cases among children in Japan. Fourth, although the timing of antiviral administration