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Clinical Infectious Diseases 2010; 51(8):990–993

1058-4838/2010/5108-0025$15.00
DOI: 10.1086/656442

Fatal Cases of Pandemic (H1N1) 2009 Influenza despite Their Early Antiviral Treatment in Japan

Neuraminidase inhibitors, including oseltamivir and zanamivir, are currently used for treatment of influenza infections. These drugs are also considered to be effective against pandemic (H1N1) 2009 influenza. It is recommended that antiviral drugs should be given especially to patients who are at increased risk of developing complications [1]. In Japan, neuraminidase inhibitors have been widely used, even for seasonal influenza and most cases of pandemic (H1N1) 2009 influenza. We assessed the timing of the antiviral treatment and the patient outcome by comparing fatal cases and severe but nonfatal cases of pandemic (H1N1) 2009 influenza in Japan. During the pandemic, fatal and severe cases were reported to the Ministry of Health, Labour, and Welfare (MHLW). At the same time, the clinical manifestation and clinical course of these cases were posted on the MHLW Web site. A severe case was defined as a patient who required admission to the intensive care unit (ICU) or who required mechanical ventilation. Both fatal and severe cases were confirmed as pandemic (H1N1) 2009 influenza by use of real-time reverse-transcription polymerase chain reaction. We included all 198 fatal cases that were reported from 15 August 2009 (when the first case was reported) through 15 March 2010. We also included 56 severe cases that were reported from 5 August through 11 October 2009, because the MHLW stopped reporting severe cases in mid-October.

Of 198 fatal cases, 158 (80%) were reported to have received antiviral treatment; of 56 severe cases, 42 (75%) were reported to have received antiviral treatment. We evaluated the timing of the antiviral treatment after the onset of symptoms between the 2 groups. As a result, the median time from the onset of illness to the initiation of antiviral drugs was 1 day for both groups, with a range of 0–18 days for fatal cases and 0–7 days for severe cases. Furthermore, 104 (66%) of 158 fatal cases and 30 (71%) of 42 severe cases have received antiviral drugs on day 0 or 1 after their onset of symptoms (Figure 1).

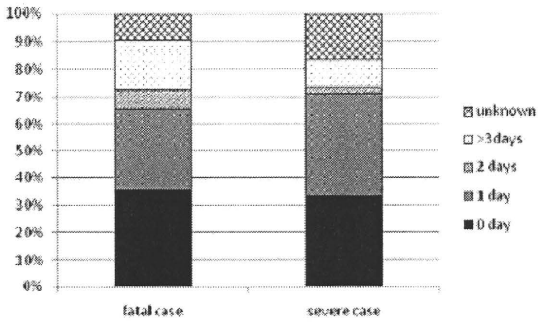

Figure 1. Duration between onset of illness and initiation of antiviral drugs. Both fatal and severe cases were confirmed as pandemic (H1N1) 2009 influenza by use of real-time reverse-transcription polymerase chain reaction. We included 158 fatal cases in patients who received antiviral treatment among all 198 fatal cases that were reported from 15 August 2009 (when the first case was reported) through 15 March 2010. We also included 42 severe cases in patients who received antiviral treatment among all 56 severe cases that were reported from 5 August through 11 October 2009, because the Ministry of Health, Labour, and Welfare stopped reporting severe cases in mid-October.

Available evidence suggests that early treatment with oseltamivir for patients with pandemic (H1N1) 2009 virus infection may reduce the duration of hospitalization [2] and the risk of progression to severe disease requiring ICU admission or resulting in death [3–5]. In Japan, during the early stage of illness, patients with symptoms of influenza-like illness tend to visit health clinics and start antiviral treatment promptly. We could not see any significant difference between fatal and severe cases in the timing of antiviral treatment after symptom onset. In Japan, where most of the patients had access to early antiviral treatment and hospital care, most of the fatal cases had also received early antiviral treatment. In other countries, those patients who received early antiviral treatment might also have received early hospital care, which can be a potential bias in assessing the impact of antiviral treatment. Although our observational data do not provide direct evidence of the effectiveness of antiviral treatment, our data clearly indicate that some severe cases had fatal outcomes despite their early treatment with antiviral drugs. More data are needed to define the exact impact of early antiviral treatment on outcome of influenza infections, including pandemic (H1N1) 2009 influenza.

Acknowledgments

Potential conflicts of interest. All authors: no conflicts.

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Version 2. PLoS Curr. 2009 December 23 [revised 2011 February 8]; 1: RRN1139.
doi: 10.1371/currents.RRN1139.

PMCID: PMC2797432
Other versions

Influenza

Epidemiological characteristics and low case fatality rate of pandemic (H1N1) 2009 in Japan

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Accepted December 22, 2009.

Abstract

Pandemic (H1N1) 2009 has been causing large outbreaks in Japan. Yet, the case fatality rate (CFR) remains low and only 85 deaths have been confirmed as of December 17, 2009. Surveillance data was analyzed to define epidemiological characteristics of pandemic (H1N1) 2009 in Japan. It was shown that most of the reported influenza-like illness cases and hospitalizations have occurred in those aged 5–9 years and 10–14 years, in whom CFR is extremely low. However, CFRs are higher in small children (<5 years) and adults. The transmission to these age groups may possibly have been minimized through aggressive suspension of classes in schools.

Introduction

Pandemic (H1N1) 2009 (pandemic H1N1) has been spreading worldwide since the first cases were identified in the United States and Mexico in April 2009 [1] [2]The H1N1 virus had caused significant outbreaks in most southern hemisphere countries between May and September 2009. As of early December 2009, it has been spreading in northern hemisphere countries. The case fatality rate (CFR) of pandemic H1N1 was initially estimated to be about 0.4% [3] However, the recent estimate is significantly lower than the initial estimate [4]. Moreover, CFR appears to be different between countries. The World Health Organization (WHO) compared the mortality rates among different countries based on the available data as of early November 2009 [5]. The mortality rates (deaths per million population) ranged from 2.2 to 3.3 in northern hemisphere countries, except in Japan, where the mortality rate was 0.2. In the United States, it is estimated that about 9820 deaths have occurred among 47 million cases [6]. On the other hand, the Ministry of Health, Labour and Welfare (MHLW) of Japan confirmed only 85 deaths as of December 1, 2009, although the estimated number of cases was about 12.6 million by the end of November (week48) [7]. It is widely believed that the low CFR in Japan resulted from aggressive early treatment with antiviral drugs such oseltamivir and zanamivir. In this study, we describe the unique epidemiological characteristics of pandemic H1N1 in Japan, which may be another important factor for low CFR in Japan.

Age Distribution of Cases, Hospitalized Cases, and Deaths in Japan

In Japan, there are about 3000 pediatric and 2000 adult outpatient clinics participating in the influenza sentinel

surveillance system that report weekly the number of influenza-like illness (ILI) stratified by age group. Between weeks 28 and 48 of 2009, 1,272,725 ILI cases were reported through the sentinel surveillance system, and it is estimated that 12.6 million people with ILI had visited outpatient clinics [7]. During this period, more than 99% of influenza viruses isolated in Japan were pandemic H1N1. Therefore, it can be assumed that majority of ILI cases during this period were caused by pandemic H1N1.

Figure 1. (a) Reported cases of influenza-like illness and rate per 100,000 between week 28 and week 48, 2009 in Japan (Upper). (b) Number of hospitalized cases and hospitalization rate per 100,000 (as of 2 December) (Lower)

Figure 1 shows the age distribution of ILI cases. In all, 1,125,907 ILI cases (88.5%) had occurred in persons younger than 20 years. In other countries, a higher incidence rate was also observed in younger age groups. However, the incidence in older age groups is much lower in Japan than in other countries. Table 1 compares the age distribution patterns of ILI cases between the United States and Japan for pandemic H1N1. Data for the United States was obtained from the Centers for Disease Control and Prevention (CDC) website [8], and Japanese data was obtained from the MHLW website [7]. It is difficult to compare the data directly from ILI surveillance between countries because the systems, including the age groups used for reporting, are different. However, there are some obvious differences between the United States and Japan. First, the proportion of ILI cases in those aged 0–4 years was lower in Japan, and cases in adults were also significantly lower in Japan; more than 75% of cases have occurred in those aged 5–19 years.

Table 1. Number of reported influenza-like illness (ILI) cases for pandemic (H1N1) in US and Japan and seasonal influenza for 2007-8 and 2004-5 influenza seasons in Japan.

Table 1 also includes data for the 2004–5 and 2007–8 influenza seasons in Japan. The predominant strains were H3N1 and influenza B for the 2004–5 season and seasonal H1N1 for the 2007–8 season. In both seasons, the proportions of small children (<5 years old) and adults (≥20 years old) with ILI were higher than those for pandemic H1N1 in Japan. Actually, the age distribution patterns in these seasons are more similar to those for pandemic H1N1 in the United States.

Enhanced surveillance of hospitalized cases of pandemic H1N1 has been implemented in Japan since July 2009. Testing with a real-time polymerase chain reaction (PCR) is being conducted for all hospitalized cases with suspected pandemic H1N1 to confirm infection; positive cases are reported to the MHLW. As of December 2, 2009, 10,487 hospitalized cases have been reported to the MHLW [9]. Figure 2 shows the number of hospitalized cases and the hospitalization rate per 100,000 population by age groups. Again, the number of hospitalized cases was highest among those aged 5–9 years, and very low hospitalization rates were observed among adult age groups. In all, 4725 hospitalized cases (45.1%) have occurred in children aged 5–9 years, and 1929 (18.4%) in those aged 10–14 years. In New South Wales, Australia, 1214 hospitalized cases had been identified by August 31, 2009 [10]. Only 69 (5.7%) patients were aged 5–9 years, and 44 (3.6%) were aged 10–14 years. The data of hospitalized cases in the United States between April and June 2009 also indicated that only 11% of total hospitalized cases were aged 5–9 years [11].

Figure 2. Number of influenza-like illness (ILI) cases reported from sentinel sites in Japan from week 28 to week 48, 2009

Table 2. Number of deaths due to pandemic (H1N1) and mortality rates per 1 million population, 100,000 estimated influenza-like illness cases (i.e. case fatality rate) and 100 hospitalizations in Japan.

As of December 1, 85 deaths had been confirmed in Japan [9]. Among 85 fatal cases, 28 (32.9%) were younger than 20 years (Table 2). In other countries, the proportion of deaths in children is much smaller. In New South Wales, Australia, only one child death occurred among 48 deaths, and the other 47 deaths occurred in those ≥20 years [10]. In California, among 118 deaths, only 8 (6.8%) were younger than 18 years [12]. The mortality rates per 1 million population, per 100,000 estimated cases, and per 100 reported hospitalized cases are also shown in Table 2. The

mortality rate per 1 million population was highest in the 0–4-year group, followed by the 5–9-year group and over 70 years. On the other hand it was lowest in the 15–19-year group. The mortality rates per estimated cases and per reported hospitalizations were very low among age groups of 5–9 years, 10–14 years, and 15–19 years. These mortality rates were higher in children aged 0–4 years than in older children. Moreover, the mortality rates, both per estimated cases and per reported hospitalizations, increased significantly with age in adults. The mortality rate per estimated cases in the 50–59-year group was more than 100 times higher than that in the 15–19-year group. The mortality rates per hospitalization were also much higher in adults, particularly in those ≥40 years. Our data indicate that CFR in small children (i.e., <5 years) and adults, especially the elderly, are higher than among those aged 5–19 years. However, most of the infections to date have occurred in these age groups (i.e., 5–19 years), while infections in other age groups are still very limited. This may be one possible reason why the CFR in Japan remains low.

School closures and epidemiological characteristics

In the previous section, we showed that the epidemiological characteristics of pandemic H1N1 are unique in Japan, which may have kept the CFR low. The main question arises: why are there unique epidemiological characteristics in Japan? The majority of cases have occurred in age groups of 5–9 years and 10–14 years (Figure 1). In general, children in primary school are aged between 6 and 12 years, and those in junior high school are aged between 13 and 15 years. Therefore, the current age distribution of cases indicates that the majority of pandemic H1N1 cases in Japan have occurred among children in primary and junior high schools. Both pandemic and seasonal influenza outbreaks often start as school outbreaks, which often become a trigger for community outbreaks. This is why early school closures or suspension of classes can be effective in reducing transmission into the community [13]. In Japan, suspension of classes is commonly implemented even for seasonal influenza [14]. For example, during the 2006–7 influenza season, 14,103 institutions (including day care centers, kindergartens and primary, junior high, and high schools) suspended classes [15]. An even more aggressive suspension of class policy has been implemented for pandemic H1N1 in 2009. Between October 25 and December 5, 2009, 94,781 institutions had implemented suspension of classes [16]. On the other hand, the CDC of the United States is not recommending such aggressive measures in the school setting [17].

Figure 2 shows the numbers of reported ILI cases by age groups in Japan. The numbers of cases among children aged 5–9 years and 10–14 years increased sharply after week 40. The highest number of cases occurred in week 44 for children aged 10–14 years and in week 47 for those aged 5–9 years, which had the highest peak on week 48. On the other hand, the number of cases in children aged 0–4 years has been increasing, particularly after week 43, and the number in adult age groups has been increasing even after week 47. These findings suggest that outbreaks in primary and junior high schools had already reached the peak by week 47, but until about week 42, the transmission into households may have been minimized by suspending classes early. However, it appears that the transmission occurring outside schools, including within households, are increasing. We have proposed the concept that with progression of outbreaks of pandemic H1N1 the incidence frequency of the outbreak shifts from schools to community, which may increase the occurrence of more severe cases and deaths resulting in higher CFR [18].

Discussion

In Japan, despite a widespread transmission of pandemic H1N1, the CFR is still low. It is widely believed that the low CFR in Japan resulted from early treatment with antivirals. In fact, Japanese physicians frequently prescribe neuraminidase inhibitors (oseltamivir or zanamivir) even for seasonal influenza. The majority of pandemic H1N1 cases are likely to have received neuraminidase inhibitors in Japan. The MHLW published the data on severe cases on November 20, 2009 [19]. They analyzed 50 fatal cases in Japan and found that 26% of fatal cases received antiviral treatment on the day of onset and 30% on the day following onset of illness. This data suggests that even early treatment with antivirals cannot prevent a fatal outcome in some cases. There is also a recent debate that questions the effectiveness of neuraminidase inhibitors in reducing complications for seasonal influenza [20],[21]. Currently available evidence on effectiveness of neuraminidase inhibitors to reduce severity of pandemic H1N1 is also not very strong, and all data are based on observational findings [22]. For example, it has been shown that hospitalized cases who received early treatment were less likely to require intensive care or were less likely to die [12]. However, those

who received early treatment may have had a different demographic background, or may also have received other supportive care, such as oxygen therapy, early enough to prevent severe complications. Further studies are needed to define the effect of neuraminidase inhibitors in reducing the severity of pandemic H1N1. At present, it is not possible to conclude that neuraminidase inhibitors are effective in reducing severe infection of pandemic H1N1 solely because of the low CFR in Japan, where neuraminidase inhibitors are used extensively.

In this study we have discussed another possible reason for the low CFR in Japan. Epidemiological characteristics of pandemic H1N1 in Japan are, to date, unique. Most cases and hospitalizations have occurred in those aged between 5 and 14 years. Children in these age groups are highly susceptible to infection of pandemic H1N1, but they are less likely to develop severe complications, and the CFR is extremely low. On the other hand, severe complications are more common in smaller children aged <5 years and adults aged ≥30 years, particularly in the elderly. However, the attack rate in these age groups is relatively low in Japan. It is still not clear what has produced this epidemiological pattern in Japan. The measure to aggressively suspend classes in schools may have contributed to a reduction in transmission into the community. However, cases in smaller children and adults are gradually increasing. More recent data indicated that the number of deaths particularly in adult patients was increasing. By December 17, 2009, according to the MHLW, 122 deaths have been confirmed in Japan. Among these cases, 37 died in December, 29 (78%) of whom were older than 40 years. This data suggests an increasing trend toward fatal cases in the adult population. The overall mortality impact in Japan may depend on how infections are spreading in different age groups in coming months.

Funding Information

Funding was provided in part by research project for emerging and re-emerging infectious diseases, Ministry of Health, Labour and Welfare, Japan.

Competing Interests

All of the authors declare that no competing interests exist.

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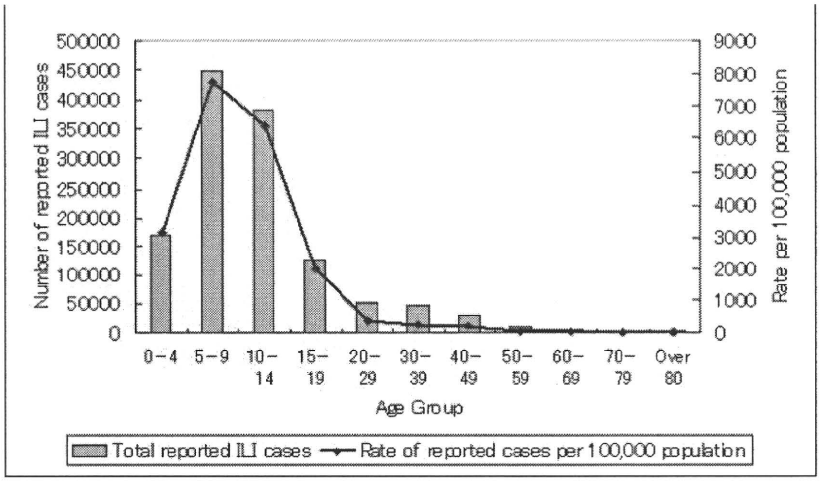
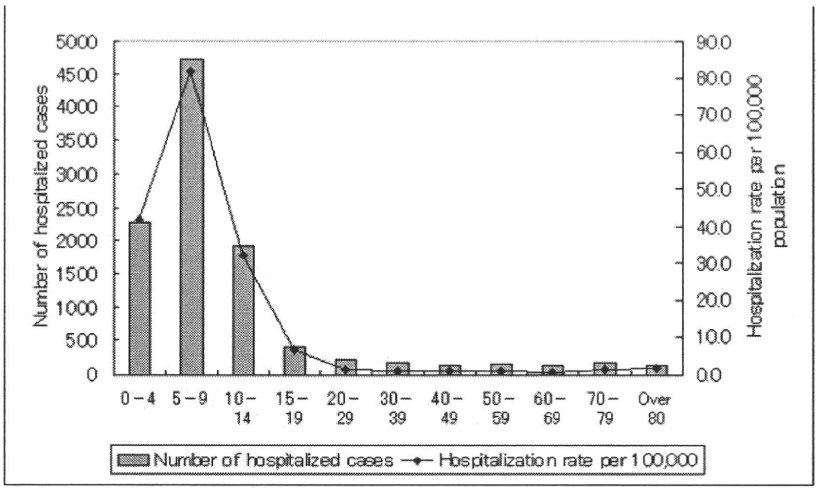
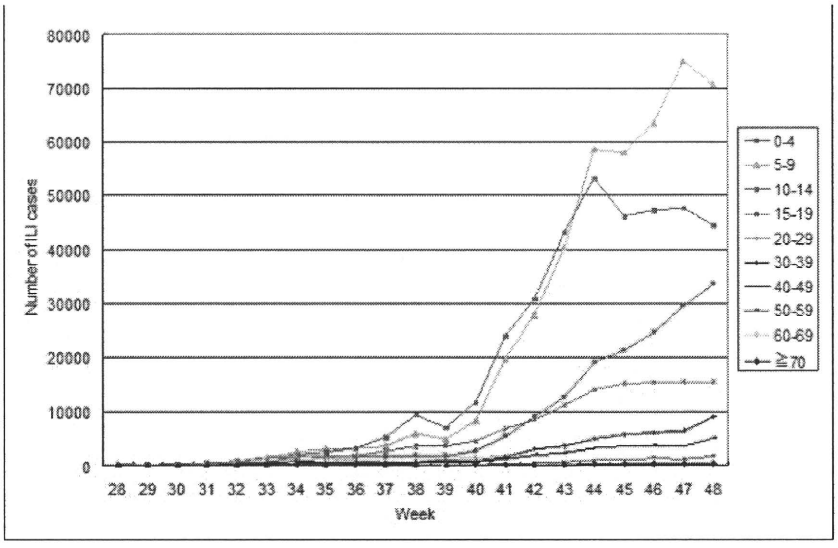
Figures and Tables




Number of hospitalized cases
Hospitalization rate per 100,000 population
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0.0
0-4
5-9
10-14
15-19
20-29
30-39
40-49
50-59
60-69
70-79
Over 80
Number of hospitalized cases
Hospitalization rate per 100,000

Country	US			Japan								
Weeks	Week 40- Week 46, 2009			Week 26 - Week 49, 2009			Week 3 - Week 18, 2005			Week 27, 2007 - Week 13, 2008		
Types	Pandemic (H1N1) 2009			Pandemic (H1N1) 2009			Seasonal H3N2 and B			Seasonal H1N1		
Age Group		Number of ILI cases	%		Number of ILI cases	%		Number of ILI cases	%		Number of ILI cases	%
	0-4	71592	21.0%	0-4	0	0.0%	0-4	371485	26.5%	0-4	160521	25.2%
	5-24	185472	54.5%	5-19	0	0.0%	5-19	646439	46.1%	5-19	344238	54.0%
	25-49	61009	17.9%	20-49	0	0.0%	20-49	277518	19.8%	20-49	113056	17.7%
	50-64	16134	4.7%	50-69	0	0.0%	50-69	78906	5.6%	50-69	16005	2.5%
	Over 65	6418	1.9%	Over 70	0	0.0%	Over 70	29064	2.1%	Over 70	4138	0.6%
	Total	340625	100.0%	Total	0	0.0%	Total	1403412	100.0%	Total	637958	100.0%



Age Group	Number of Deaths	Percentage (%)	Mortality rate per 1 million population	Mortality rate per estimated 100,000 cases	Mortality rate per 100 hospitalizations
0-4	11	12.9	2.04	0.92	0.48
5-9	8	9.4	1.38	0.24	0.17
10-14	4	4.7	0.67	0.11	0.21
15-19	1	1.2	0.16	0.05	0.24
20-29	4	4.7	0.27	0.39	1.90
30-39	8	9.4	0.43	1.05	4.60
40-49	10	11.8	0.62	1.98	6.94
50-59	10	11.8	0.57	5.27	6.17
60-69	9	10.6	0.53	11.87	6.34
Over 70	20	23.5	0.99	31.65	6.35
Total	85	100.0	0.67	0.67	0.81

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Available online 14 January 2008

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doi:10.1016/j.jhin.2007.11.001

Infection and its control in group homes for the elderly in Japan

Madam,

Following the implementation in Japan of a new, long-term care insurance system in April 2000, the number of small-scale facilities known as group homes has risen rapidly to more than 6000. These homes, which provide an alternative to traditional, larger-scale long-term care facilities for elderly demented people, are regulated by the municipality. The municipality is responsible for assigning, supervising and instructing all group home employers. Compared with care at traditional, larger-scale facilities, care at small-scale group homes is believed to treat patients better primarily in terms of dementia symptom management and minimizing functional decline.

Recently, mass outbreaks of influenza and norovirus in senior care facilities have been reported in many regions.[1–3] Small-scale facilities have paid less attention to infection control than large-scale ones and were unequipped with manuals outlining policies for the prevention of infectious diseases. Therefore, we examined the actual conditions of infection and the systems of infection control in small-scale care facilities in Japan.

Questionnaires were sent to 1899 care facilities registered with the National Association of Dementia Group Homes throughout Japan to investigate infection control measures at each facility. Discussions were held with community-based service representatives, including municipal supervisors and instructors as well as infection control specialists; and inspections of small-scale multifunctional group homes, dementia group homes, and group homes for fewer than 29 people needing heavy care were conducted to examine the current situation from multiple perspectives.

In all, 684 facilities (36%) completed the questionnaires. As shown in Figure 1, 26% of facilities had residents who had been infected with influenza, 14.5% with scabies, 12% with norovirus and 8.2% with meticillin-resistant *Staphylococcus aureus* (MRSA). These four communicable diseases were frequently found in residents. The mass outbreaks

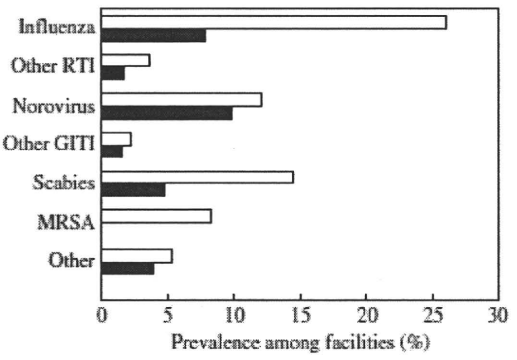

Figure 1 Prevalence of infections and outbreaks among the facilities. Open bars show the prevalence of facilities which had residents who suffered from the infection indicated. Closed bars show the prevalence of facilities which experienced mass outbreaks of infection indicated. 'Other RTI' denotes respiratory tract infections other than influenza and meticillin-resistant *Staphylococcus aureus* (MRSA). 'Other GITI' denotes gastrointestinal tract infections other than norovirus and MRSA. 'Other' denotes infection in organs other than the respiratory tract and the gastrointestinal tract.

reported in these facilities were norovirus (9.8%), influenza (7.9%) and scabies (4.7%) (Figure 1). Influenza vaccination was provided to all employees and residents upon request, in most facilities. Although facilities did not experience any mass outbreaks of MRSA, the procedures to cope with MRSA differed among facilities; 10.1% failed to address MRSA, 3.9% isolated infected/colonised individuals in a room while 3.5% used gowns and pre-prepared disinfectant. Regarding the response following norovirus infection, 90.1% of facilities used gloves but only 60.1% used masks when disposing of vomit. In all, 26.9% of facilities kept pets, 11.6% kept dogs, 4.7% kept cats and 0.3% kept reptiles that are known to be carriers of *Salmonella* spp. Although most facilities reported policies addressing the collection of bodily fluids, blood and faeces for disposal, no standardized policies outlining final disposal methods were reported; 60% of facilities disposed of them as general refuse. Oral care, which is considered to have an effect in preventing pneumonia, was done regularly by dentists or hygienists in 22.4% of facilities. It was also revealed that even though many facilities implemented response measures to stop the spread of influenza, they experienced mass outbreaks of norovirus, influenza and scabies. Improvement is needed especially in the disposal of infectious waste since many facilities did not use masks when disposing of norovirus vomit.

We conclude that improvement in the management of infectious disease in small-scale facilities for elderly people in Japan is needed. The problems highlighted in this research show the need for developing standardized infectious disease control strategies and for creating a manual that outlines detailed measures designed to specifically meet the needs of small-scale group homes in Japan.

Conflict of interest statement
None declared.

Funding sources
Grant from the Ministry of Health, Labor and Welfare.

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Available online 16 January 2008

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doi:10.1016/j.jhin.2007.11.009

Meticillin-resistant *Staphylococcus aureus* in the community: homeless are also at risk

Madam,

Thomas *et al.* recently identified the district nurse population as a significant reservoir for meticillin-resistant *Staphylococcus aureus* (MRSA) in the community, with 21.1% [confidence interval (CI): 11.6–30.4] of the study population found to be MRSA positive.[1] Other population groups known to be at risk of community MRSA colonisation or infection include military recruits, sports teams players, men who have sex with men, people in jail, injecting drug users (IDUs) and the homeless. Current or past IDUs and a history of skin abscess is associated with a higher prevalence of meticillin resistance in those who are *S. aureus*-colonised.[2–5] Studies from the USA have shown that the homeless are at a significantly increased risk (odds ratio: 3.35; 95% confidence interval: 1.22–9.22) of community-acquired MRSA skin and soft tissue infections compared with the non-homeless.[3,4] To our knowledge, we present the first assessment of skin and soft tissue infections due to MRSA in people who are homeless or at risk of homelessness in the UK.

We identified all wound swabs routinely submitted to the Health Protection Agency Regional Microbiology Laboratory in Cambridge over a period of four years (3 August 2003 to 3 August 2007) from

原　著

拡大サーベイランスに基づく長野県佐久地域の2008/09シーズンにおけるインフルエンザ様患者数に関する検討

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（平成22年1月7日受付）
（平成22年6月7日受理）

Key words: influenza, influenza-like illness, outpatients, surveillance, disease burden

要　旨

内科や小児科を標榜する病院や診療所に毎年多くのインフルエンザ様患者が受診をしている．しかし，それらのインフルエンザ患者報告数は定点医療機関からの情報に基づいているため，実際のインフルエンザ感染者の全体像を反映しているか不明である．そこで2008/09シーズンの長野県佐久地域における非定点医療機関を含む医療施設でのインフルエンザ様疾患（ILI）の受診に関する検討を行った．その結果，ILIは内科や小児科を標榜する医療機関の他に耳鼻咽喉科にも認められた．さらに，全ての調査施設から推定されたインフルエンザ受診者は2,415人であり人口の約1.14%，定点医療機関からのILI報告数に基づく推定値は同疫学週で2,862人であり人口の約1.35%であった．インフルエンザ受診者数の推定値は，本調査における推定値よりも定点医療機関の推定値が約18.5%高かった．定点医療機関からの推定値は医療施設の特性別に小児科病院1,020人，内科診療所（主な診療科目が小児科以外）1,674人であった．しかし，我々の調査によるインフルエンザ推定受診者数は小児科病院503人，内科診療所（主な診療科目が小児科以外）741人であり，定点医療機関からの推定値の約半数であった．これらの差は定点医療機関に，より多くのILI患者が受診しているためであると考えられる．また，医療施設の特性において医療機関として内科だけを標榜する病院と診療所（小児科を有しない）が佐久地域では定点医療機関としては含まれていない．しかし，今回の調査では同カテゴリーの医療機関においてインフルエンザ受診者数の推定は967人であった．さらに，耳鼻咽喉科診療所のインフルエンザ受診者の推定は71人であった．インフルエンザ受診患者の推定値は医療施設の特性ごとに差を生じており，医療施設の特性ごとにILIによる医療負荷を検討する必要性が示唆された．

〔感染症誌　84：575～582，2010〕

序　文

インフルエンザは日本において冬季に流行しており，多くの場合に急性呼吸器症状を呈して数日で寛解するが，高齢者や基礎疾患を有した患者では重症化することもある急性ウイルス性疾患である．日本ではインフルエンザに関連した超過死亡が約1万人と推定され[1]，公衆衛生上重要な疾患である．

1999年4月より「感染症の予防及び感染症の患者に対する医療に関する法律」（感染症法）が施行され，インフルエンザは5類感染症として全国の小児科約3,000と内科約2,000からなるインフルエンザ定点医療機関から週毎に患者数が報告されている[2]．これまで，インフルエンザサーベイランスによる定点医療機関から報告された患者数および医療統計による医療施設属性と施設数から演繹してインフルエンザ推定患者数が算出されてきた[3,4]．しかし，この方法による推定は定点医療機関が均一に分布しているという前提条件によるものであるために，定点医療機関に偏りが存在する場合には推定値に誤差が生じる．また，小児科・内科以外の診療科への受診については検討されていないことから，推定値の過大評価や過小評価になる可能性があると考えられる．

我が国は保険診療でかつ，抗インフルエンザ薬によ

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平成22年9月20日

Table 1 Total facilities and number of investigated facilities

Influenza healthcare facilities	Sentinel		Non-sentinel		Total
	surveyed	not surveyed	surveyed	not surveyed	
Hospitals	3	0	5	6	14
Clinics	5	1	22	108	136
Total	8	1	27	114	

る治療が一般的であることから[5]，医療機関への受診行動が米国などと異なると考えられる．そこで季節性インフルエンザの受診者数を調査することで，様々な医療機関に対するインフルエンザ受診患者の動向とともに推定患者数に関する検討を目的として，2008/09シーズンにおける季節性インフルエンザの受診動向を調査した．今回の調査後に新型インフルエンザA（H1N1）が発生し，2009年6月11日に世界保健機構（WHO）がフェーズ6を宣言した．今回の調査結果は，このような新型インフルエンザによる被害を想定する際の基礎資料となることも期待される．

対象と方法

1. 対象地域

長野県佐久市，小諸市，南佐久郡，北佐久郡を含む医療圏には人口212,193人（平成21年4月1日現在）が含まれる．同医療圏には病院14施設，診療所136施設があり，インフルエンザ定点医療機関は9施設である．調査協力の得られたインフルエンザ定点医療機関8施設，非定点医療機関27施設を対象とした（Table 1）．調査対象医療機関の標榜診療科は，内科，小児科，耳鼻咽喉科，産婦人科，皮膚科，外科であった．

2. 調査方法

医療機関へのインフルエンザ受診者数の調査開始は，長野県感染症発生動向調査を参考にしてインフルエンザ定点あたり報告数が10を越えた疫学週から開始することとしたが，実際には第5疫学週（2009年1月26日～2月1日）からデータ収集を開始した．その際のインフルエンザ定点あたり届出数は47.13であった．また定点あたり報告数が10以下となったことを受けて第14疫学週（2009年3月30日～4月5日）に調査を終了した．調査協力の得られた対象施設では，週毎のILI患者数とその年齢階層および性別，総外来者数とその年齢階層に関して集計用紙を用いて収集した．

3. インフルエンザ診断の定義

感染症法のインフルエンザ届出基準に基づき，突然の発症，38℃を超える発熱，上気道炎症状，全身倦怠感等の全身症状を呈した場合または咽頭ぬぐい液，鼻腔ぬぐい液，鼻腔吸引液からインフルエンザ簡易キットによりインフルエンザウイルスの抗原が検出された人とした．

4. 解析方法

回収したデータから疫学週あたりのILI患者数と総外来者数をそれぞれ求め，さらにインフルエンザ定点医療機関と非定点医療機関，年齢階層，性別に分けて患者数を集計した．さらに標榜診療科，病院規模（病院または診療所）別に実数および総外来者数に占めるILI患者数の割合を算出した．

5. インフルエンザ受診者の推定

インフルエンザ受診者の推定のためにiを調査対象施設とし，それぞれの医療施設の特性におけるILI患者数をXikとした．医療施設の特性は5つに分け，k＝1：小児科を有する病院，k＝2：小児科を有する診療所（主な診療科が小児科），k＝3：小児科を有する診療所（主な診療科が小児科以外），k＝4：内科を有する病院と診療所（小児科を有しない），k＝5：耳鼻咽喉科を有する診療所（内科と小児科を有しない）とした．それぞれの医療施設の特性におけるILI患者数の平均値を算出するために

$$Mk = \frac{\sum_{i} Xik}{\sum_{i} i}$$

とおき，それぞれの医療施設の特性に存在する全医療機関数をvkとした．そしてインフルエンザ受診者の推定値＝$\Sigma_k vk \cdot Mk$とすることで，医療施設の特性ごとのILI患者数の平均値をそれぞれのカテゴリーにある全医療機関数に乗じてインフルエンザ受診者数の推定を行った．あわせて95%信頼区間を算出して検討を行った．

結　果

1. 佐久地域におけるILI患者受診数の動向

今回調査した佐久地域におけるインフルエンザ受診者の動向を，インフルエンザ定点医療機関と非定点医療機関に分けてFig. 1に示した．2008/09シーズンは第5疫学週にピークをむかえ，さらに第12疫学週にインフルエンザ定点医療機関を中心とした流行を認めた．なお長野県環境保全研究所から報告されているインフルエンザの分離状況を考慮し第5疫学週のピークにA型インフルエンザ，第12疫学週にはB型インフルエンザを中心とした流行が起きていたと考えられた．

2. ILIの年齢階層と性差

医療施設の特性を基に，小児科を有する病院と診療

Fig. 1　Influenza-like illness (ILI) number from 5 to 14 weeks in Saku area, in 2008-09 season

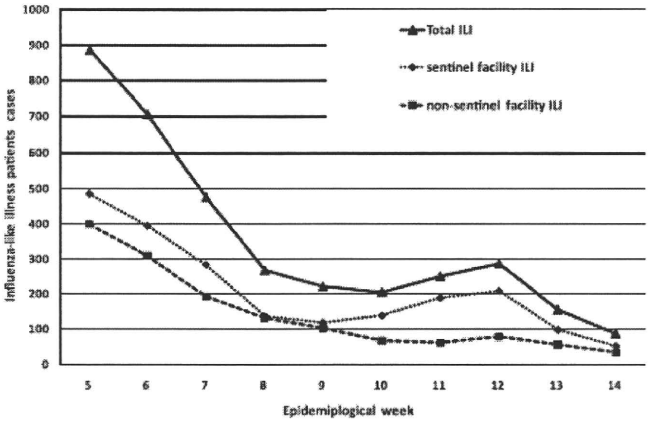
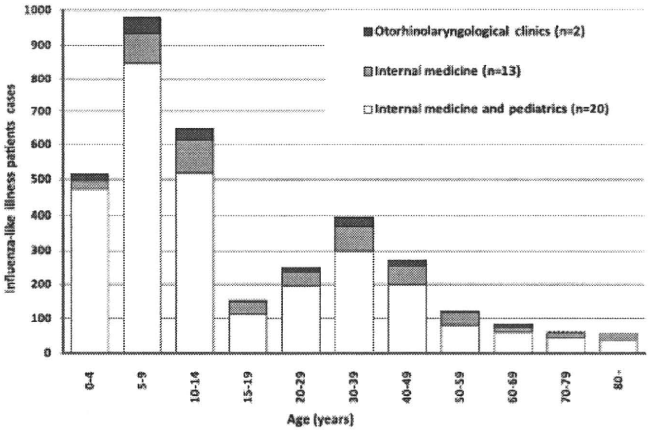


Fig. 2　Influenza-like illness (ILI) patient age at different healthcare facilities, i.e., otorhinolaryngological clinics, internal medicine, and pediatrics.



所，内科を有する病院と診療所(小児科を有しない)，耳鼻咽喉科を有する診療所のグループにおける年齢階層別のインフルエンザ患者数を示した（Fig. 2）．今回の調査で合計3,539人のILIがみられ，年齢階層別にみると小児期では5～9歳が978人（27.63%），成人期では30～39歳が396人（11.19%）と最も多かった．また，季節性インフルエンザ患者数が多い[57]とされる14歳以下は，調査期間内で合計2,140人（60.47%），インフルエンザピークを迎えた第5疫学週で479人（54.19%），第2のピークを迎えた第12疫学週で223人（78.80%）であり小児の患者が多数を占めていた．さらに性差を検討したところ，ILIで受診すると想定される内科と小児科を標榜する診療科でのILIの男女比は20～29歳で0.83：1，30～39歳で0.74：1，40～49歳で0.79：1であり，これら以外の年齢階層においては明らかな男女差はなかった．

3．総外来受診者数に占めるILI患者数の割合

医療機関の規模により総外来受診数が異なることから，病院と診療所毎に週単位の総外来受診数に占めるILI患者数の割合を示した（Fig. 3）．インフルエンザ定点医療機関にILIが集積する傾向があり，診療所の定点医療機関5施設での総外来者数に占めるILI患者数の割合は最大で2009年第6疫学週（総外来者数1,631人，ILI数185人）に14.3%±8.7（平均±標準偏差）となり，その後は減少したが第12疫学週（総外来者数1,427人，ILI数118人）では9.0%±4.2であった．これに対し非定点医療機関の診療所では，最大で2009年第5疫学週（総外来者数6,259人，ILI数

平成22年9月20日

Fig. 3 Total influenza-like illness (ILI) patients outpatients by week, at sentinel and non-sentinel facilities.

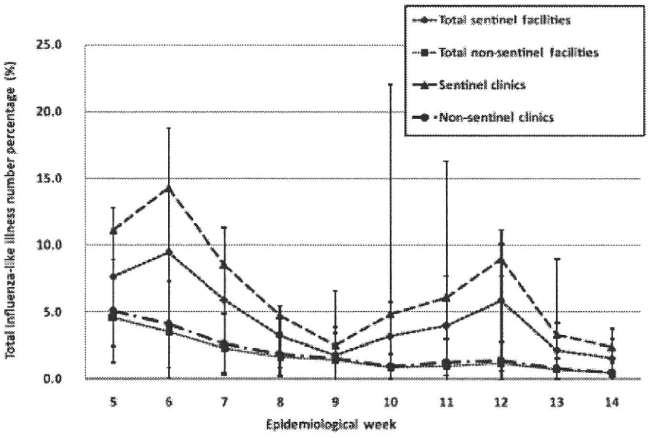
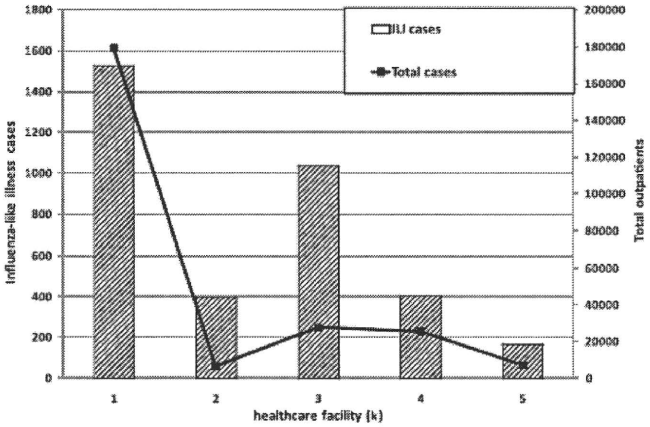


Fig. 4 Influenza-like illness (ILI) number and total outpatients at different facilities. k=1: Hospitals with pediatrics (n=8), k=2: Pediatric clinics (n=4), k=3: Clinics with internal medicine and pediatrics (n=9), k=4: Hospitals and clinics with internal medicine but no pediatrics (n=12), k=5: Otorhinolaryngological clinics (n=2).



303 人）に 5.1% ±3.9 であった．

4. 診療科別にみた ILI

標榜する診療科ごとに ILI 患者数および総外来受診者数に関して検討した（Fig. 4）．調査期間内では内科を標榜する病院と診療所に 478 名，小児科を標榜する診療所（主な診療科が小児科以外）に 423 名とともに耳鼻咽喉科を標榜する診療所に 166 名の ILI が認められ，内科や小児科以外に耳鼻咽喉科にも ILI がみられた．今回の調査では，外科や皮膚科のみを標榜する単科診療所は無かったが，これらを標榜する診療科にも少数ではあるが ILI が確認された．

5. インフルエンザ受診者数の推定

2009 年第 5 疫学週から第 14 疫学週までにおいて，佐久地域のインフルエンザ推定受診者数を検討した．全ての調査対象医療施設からの ILI 受診者数を用いた場合とインフルエンザ定点医療機関からの ILI 受診者数を用いた場合の推定を行った（Fig. 5）．調査期間における週毎のインフルエンザ受診者数の推定値と ILI の動向は同様な傾向であったことから，ピーク時の 2009 年第 5 疫学週に関して検討を行った．同疫学週において耳鼻咽喉科の診療所を含む全ての調査施設から推定されたインフルエンザ受診者は 2,415 人（95% 信頼区間：1,764～3,062 人）であり人口の約 1.14%（95% 信頼区間：0.83～1.44%）であった．ま

Fig. 5 Estimated influenza patients from sentinel and total facilities during 2008-09 season from 5 to 14 weeks.

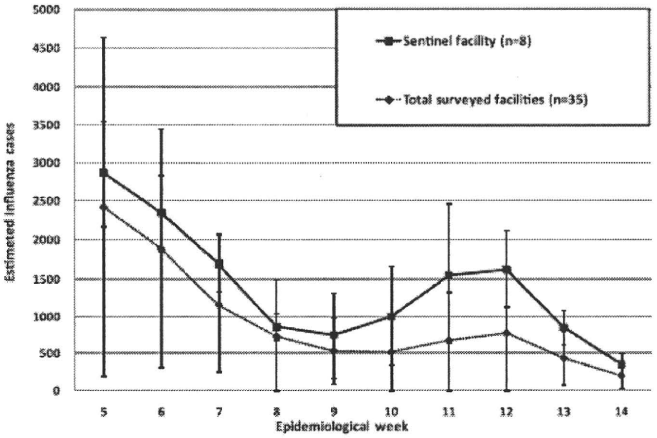


Table 2 Estimated influenza number for different facilities and for sentinel and total facilities during week 5, 2009. Total surveyed facilities included otorhinolaryngology clinics. "(n =)" number of facilities when estimated of influenza cases.

Surveyed facilities	Total	Sentinel
Hospitals with pediatrics	503 (n = 8)	1,020 (n = 3)
Pediatric clinics	133 (n = 4)	168 (n = 3)
Non-pediatric clinics	741 (n = 9)	1,674 (n = 2)
Hospitals and clinics with internal medicine but no pediatrics	967 (n = 12)	no data
Otorhinolaryngological clinics	71 (n = 2)	no data
Total estimated influenza cases and interval estimation	2,415 1,764－3,062	2,862 2,175－3,549

た，定点医療機関からのILI報告数に基づく推定値は同疫学週で2,862人（95% 信頼区間：2,175～3,549人）であり人口の約1.35%（95% 信頼区間：1.03～1.67%）であった．インフルエンザ受診者数の推定値において，定点医療機関からの推定値は非定点を含む推定値よりも約18.5% 高かった．そこで，医療施設の特性毎にインフルエンザ受診者数の推定値をTable 2に示した．

定点医療機関からの推定値は医療施設の特性別に小児科病院1,020人，内科診療所（主な診療科目が小児科以外）1,674人であった．しかし，我々の調査によるインフルエンザ推定受診者数は小児科病院503人，内科診療所（主な診療科目が小児科以外）741人で定点医療機関からの推定値の約半数であった．小児科病院のカテゴリーにおいて定点医療機関は2施設であるが，本調査では8施設を対象とした．また内科診療所のカテゴリーでは定点医療機関は2施設であったが，本調査では9施設を対象としていた．さらに，佐久地域では内科だけを標榜する病院と診療所（小児科を有しない）が定点医療機関としては含まれていないが，今回の調査では同カテゴリーの医療機関においてインフルエンザ受診者数が967人と推定されている．さらに耳鼻咽喉科診療所では71人のインフルエンザ受診者数が推定されている．

考　察

長野県感染症発生動向調査より2009年第5疫学週と第12疫学週にインフルエンザ患者数のピークがあり，本調査においても同週にピークを認め，第5疫学週にA型インフルエンザ，第12疫学週はB型インフルエンザによる流行が起きていたと考えられる．総外来者数に占めるILI患者数の割合は，定点医療機関の診療所で最大で第6疫学週に14.3% であった．インフルエンザ非定点医療機関においてもILIは認められたが，定点医療機関と比較するとILI患者が集中する度合いが小さい傾向にあった．病院と診療所では診療科目数が異なり総外来者数が異なることから，内科や小児科を標榜するインフルエンザ定点の診療所は相対的にILIの割合が高くなるものと考えられる．しかし，インフルエンザ非定点医療機関でのILIの推移は定点医療機関と比較して規模は小さいが，総外来者数に占めるILI患者数の割合はほぼ同じ動向を示している．新型インフルエンザA（H1N1）の流行[9]や夏季にも大流行してきた過去のインフルエンザパンデミック[10]，さらに通常の医療機関の外来受診には様々な疾患の治療や予防を目的とする患者の受診もあることから，ILI症状を呈した場合に受診する医療機関でのインフルエ

平成22年9月20日

ンザ負荷の増大を検討する必要があると考えられる．

診療科目別の検討では内科や小児科以外に耳鼻咽喉科においてもILIが確認された．一般成人がかぜ症候群や急性咽頭炎を呈した場合に耳鼻咽喉科を受診する人は33.3%であると報告されており[10]，急性呼吸器感染症であるILIで耳鼻咽喉科を受診する場合も考えられる．さらに年齢階層別にみると小児期では5～9歳と10～14歳，成人期では30～39歳にインフルエンザ患者のピークを示すとともに幅広い年齢階層においての受診があった．インフルエンザは14歳以下の小児に感染拡大しやすく[6]，この年齢層に対して一次医療を担う医療機関の確保は重要であると考えられる．さらに30～39歳を中心としたピークは労働力人口であり行動範囲が広く感染の機会が多いことに加え，親世代であることで家庭内感染の機会が多いことから[11][12]，本調査期間での季節性インフルエンザは14歳以下の小児と30歳代を中心とする成人にピークが形成されたと考察される．これらの知見は従来の季節性インフルエンザで観察された年齢構成と同様である[6][7]．さらに，本調査から男女差に関して20～29歳，30～39歳，40～49歳には女性が多い傾向があり，その要因の1つとして小児のインフルエンザが母親に家庭内感染を生じていることが考えられる[13]．家族内感染を予防するには適切な手洗いとマスク着用が効果的である[14]とされており，住民のインフルエンザ予防活動により感染の機会を減少させることも重要であると考えられる．

2009年4月よりメキシコと米国から報告された新型インフルエンザA（H1N1）の感染伝播の広がりは季節性インフルエンザと同等かそれ以上と報告されている[15][16]．また新型インフルエンザ流行時に発熱した場合は85%の人が医療機関を受診する[17]とされていることから新型インフルエンザと季節性インフルエンザが流行したときの医療機関へのインパクトならびに医療機関でのインフルエンザ感染が懸念される．医療機関への負荷を検討する指標としてインフルエンザ患者数の推定が重要であると考えられるが，推定患者数は定点医療機関からのILI報告数により算出されており非定点医療機関を受診するILI患者数は考慮されていない．さらに定点医療機関は人口に基づき選定される施設数が決まっていることから，地域での人口分布の偏りにより受診する医療機関が限定されることや受診する医療機関へのアクセスや診療時間などによる医療受診行動の2つの点で制約を強く受けていると考えられる．

我々の調査と定点医療機関によるインフルエンザ推定受診者数には18.5%の差があった．この差に統計学的有意差を認めなかったが，Table 2から定点医療機関を基にした推定値では医療施設の特性別に小児科病院と内科診療所（主な診療科目が小児科以外）が推定値の大部分を占めていた．しかし，我々の調査によるインフルエンザ推定受診者数は小児科病院と内科診療所（主な診療科目が小児科以外）において，定点医療機関との推定値と大きく異なっていた．これは本調査では，定点医療機関より多くの医療施設を対象としたことによるものと考えられる．小児科病院は管内に10施設が存在するが定点医療機関3施設の観測であるため，佐久地域においては定点医療機関にILIが集積する傾向があることから，従来の定点医療機関での観測数から管内の患者数を推定する方法では過大評価になっていると考えられる．また定点医療機関には内科を標榜する病院と診療所（小児科を有しない）が含まれていないが，我々の調査した同医療施設の特性からILIが確認されたことで，インフルエンザ推定受診者数は医療区分の中では一番大きな推定値となっている．さらに耳鼻咽喉科診療所においてもインフルエンザ推定受診者を確認している．すなわち，定点医療機関に含まれていない内科病院と診療所（小児科を有しない），および耳鼻咽喉科診療所にもILIの集積が確認されたことになる．以上のことからインフルエンザ推定受診者数に差が生じているのは，大きく分けて2つの要素が関連していると考えられる．1つ目は，定点医療機関として区分される小児科を標榜する医療機関や内科小児科診療所におけるインフルエンザ定点サーベイランスでは過大評価になっている可能性がある．第2に我々の調査で検討した内科病院と診療所(小児科を有しない）および耳鼻咽喉科診療所においてILIの集積が認められたが，この医療機関区分はインフルエンザ定点医療機関として区分されていないために，この区分を受診した患者数に関しては過小評価になっている可能性が挙げられる．よって内科や小児科を標榜する医療機関はもちろんのこと，耳鼻咽喉科などの様々な標榜科を含めた医療機関によるILI受診者数とそれに基づいた推定によって医療機関の負荷を評価することも1つの方法として考えられる．しかし，インフルエンザ定点医療機関は内科と小児科医療機関から選定されており[18]，本調査での佐久地域における定点医療機関は非定点医療機関と比較してより多くのILI患者数が認められたことを考慮すると，インフルエンザの動向を適時的に把握できると考えられる．

本研究の限界として，医療機関を受診したILI患者を対象としているためインフルエンザの確定診断を行っておらず，インフルエンザ推定受診者数は医療機関を受診したILIであり非受診者を追跡していない．また，休日や救急外来を受診しているILIも調査されていない．救急医療機関の夜間休日外来者数のうち発

熱者の占める割合は54.5%と報告されており[19]，アメリカのシカゴでの調査ではILI症状が軽度の場合52%の人しか医療機関を受診しないという報告[20]もあることから，24時間対応の救急外来や休日診療を行っている医療機関やILI症状で医療機関を受診しない人を考慮することでILIはさらに多いと予測される．さらに，今回の調査期間は2009年第5疫学週から第14疫学週であることから，それ以前の動向を捉えられていないが感染症発生動向調査での季節性インフルエンザの動向が類似しているため，本調査期間での動向は捉えられていると考える．

謝辞：本調査の遂行にあたりご尽力頂いた佐久保健福祉事務所，佐久医師会，小諸北佐久医師会，各医療機関の方々に深謝いたします．ならびにご指導頂いた東北大学大学院医学系研究科看護アセスメント学分野教授丸山良子先生に深謝いたします．

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平成22年9月20日

Epidemiological Study of Influenza-like Illness Under Enhanced Surveillance in Saku, Nagano Prefecture, Outpatients during the 2008-09 Influenza Season

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Many influenza-like illness (ILI) outpatients visit healthcare facilities such as internal medicine and pediatric clinics every year. In Japan, however, ILI is reported only by sentinel healthcare facilities. We studied the number of ILI subjects visiting sentinel and non-sentinel healthcare facilities during the 2008-09 season in Saku, Nagano prefecture, obtaining the numbers of cases from sentinel and non-sentinel facilities. Most ILI subjects visited internal and pediatric facilities, and some visited otorhinolaryngological clinics not included as sentinel sites. We also estimated the total number of influenza cases based on data from sentinel facilities and total surveyed facilities, including non-sentinel. We divided facilities into hospitals with pediatrics, pediatric clinics, internal medicine and pediatric clinics, hospitals and clinics with internal medicine but no pediatrics, and otorhinolaryngological clinics. Estimated sentinel-site ILI cases was 2,862, including 1,020 for hospitals with pediatrics and 1,674 for clinics with internal medicine and pediatrics. The estimated number of ILI cases from total facilities surveyed was significantly lower, at 503 for hospitals with pediatrics, and 741 for clinics with internal medicine and pediatrics. Estimated ILI cases from categories not including sentinel sites were 967 for hospitals and clinics with internal medicine but no pediatrics, and 71 for otorhinolaryngological clinics. The estimated number of total ILI cases differed by 18.5%, depending on facility categories. This indicates that more detailed analysis is needed to accurately estimate ILI cases.

原　著

2008～2009シーズンの庄内地域におけるインフルエンザ外来患者からみた医療施設への負荷の検討：新型インフルエンザA（H1N1）を視野に入れて

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（平成21年10月20日受付）
（平成21年12月8日受理）

Key words: Influenza, outpatient, health service burden

要　旨

これまで我が国においてインフルエンザ流行時にインフルエンザ患者がどの程度医療施設へ集積するのか分かっていない．そこで，我々は2008/09シーズンに山形県庄内地域における医療施設の外来受診状況を調査し，季節性インフルエンザによる医療施設への負荷を評価した．その結果，インフルエンザ患者受診数は病院で最も多かったが，外来受診者全体に対するインフルエンザ患者の占める割合が最も高かったのは小児科診療所であった．さらに，厚生労働省の発表した新型インフルエンザの推定発症率をもとに庄内地域における新型インフルエンザの患者発生数の推定を行ったところ発症者総数は59,600-89,400人と推定できた．今回の結果より，今冬新型インフルエンザ患者が2008/09シーズンと近い医療受療行動をとった場合，病院外来および小児科標榜診療所へ著しい負荷の増加が予想され，その対策が必要と考える．

〔感染症誌　84：52～58，2010〕

序　文

インフルエンザは急性ウイルス性の呼吸器感染症であり，世界保健機関（WHO）によると世界中で毎年250,000から500,000人の死亡者が出ていると推定されており[1]，わが国でも約10,000人の超過死亡数が報告されるなど公衆衛生上，重要な疾患である[2]．わが国の季節性インフルエンザは，北半球の多くの国と同様に毎年11月下旬から12月上旬頃に本格的な流行が始まり，翌年の1月から3月にかけてピークを迎え，4～5月に流行が終息していくという明確な季節性をもつ[3]．発熱・頭痛・全身倦怠感・筋関節痛などが出現し，咳・鼻汁などが続き，約1週間で軽快するのが典型的なインフルエンザの症状である[4]．確定診断にはウイルス学的な検査が必要であるが，咽頭拭い液や鼻腔・鼻咽頭拭い液を材料にして，ウイルス分離を行うことが標準である．治療は主としてノイラミニダーゼ阻害薬であるOseltamivirとZanamivirが用いられている．

2009年4月に新型インフルエンザA（H1N1）が報告され，その後世界各地に感染拡大した．WHOは6月11日にフェーズ6を宣言し，世界的大流行を公式に確認した．日本では5月16日に神戸で国内感染例が報告され，その後学校を中心に流行が起こり，感染拡大防止のために広範な地域において学校閉鎖などが実施された．一方でこの時期は発熱外来・発熱相談センターに対する過剰負担が指摘された期間でもある[5][6]．このように，国内感染初期段階においても診療体制の整備の遅れなどが医療施設や地方自治体に対する課題として挙げられ，これから本格的なインフルエンザの流行シーズンを迎えるにあたり大きな課題を残している．北半球にある各国では，本格的な流行を前に様々な被害想定を行っており，それを参考にして対策が立てられている．最も重要な対策の1つに医療施設における対応が挙げられており，米国ではインフルエンザの罹患者のうち医療施設へ入院する必要のある

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