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Epidemiological Report

Evaluation of a Sentinel Surveillance System for Influenza, 1995-2000, Kyoto City, Japan

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SUMMARY: We compared a municipal sentinel surveillance system for influenza with the Microbial Isolation Surveillance System (MISS) in Kyoto City, Japan. Sensitivity, specificity, and predictive value positive (PVP) of the Influenza Sentinel Surveillance System (ISSS) compared to the MISS were calculated by influenza season and by month. Sensitivity ranged from 80 to 97%, specificity ranged from 55 to 77%, and PVP ranged from 29 to 52% by season ($P < 0.001$). On the other hand, sensitivity ranged from 86 to 100%, specificity ranged from 38 to 66%, and PVP ranged from 31 to 50% by month ($P < 0.001$). Specificity was calculated as 93% in November. The sensitivity of ISSS was found to be sufficient regardless of the magnitude of influenza activity. Specificity varied by season, indicating the difficulty of clinically diagnosing other respiratory illnesses. The PVP remained at less than 50% before and after the influenza seasons and it varied year by year. In general, the ISSS is a good surveillance system for monitoring influenza activity.

INTRODUCTION

Influenza is one of the most important infectious diseases requiring surveillance in industrialized countries (1). The reported number of influenza patients from sentinel sites in Japan was 757,837 (310.59/site) during an April 1994 through March 1995 season. A total of 4,135 patients died of influenza during the period from 1995 to 1999. Actual numbers may be higher, because when a patient dies of influenza, physicians often report instead that the patient died of resultant clinical states, in particular pneumonia. In order to avoid such under-estimation of influenza in view of the disease burden, a measurement of influenza excess mortality can be useful (2,3). Approximately 29,000 (22.65 per 100,000) cases were reported in the 1998/1999 season, which was unprecedentedly high for the past decade in Japan (4). It will become increasingly important to achieve improved influenza surveillance in order to understand the subsequent disease burden of influenza, as well as to assess the effectiveness of influenza vaccinations. Because the magnitude and epidemic strains of influenza vary from season to season, serological monitoring will be necessary in order to test for a match between current vaccine strains and epidemic strains (5). However, evaluation of influenza surveillance systems is often not carried out. One reason for this is that it remains difficult to confirm infection by influenza among numerous patients with influenza-like illness (ILI) that are contracted in a short period of time.

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The Influenza Sentinel Surveillance System (ISSS) is the sole national surveillance system for influenza in Japan; this program is administered by the Ministry of Health, Labour and Welfare. In the National Epidemiological Surveillance for Infectious Diseases (NESID) program, accuracy of such data is assured by ~10% sampling for virological tests at the municipal and prefectural levels (Fig. 1).

In Kyoto City, evaluation of the ISSS has not previously been performed. Influenza activity increased remarkably during the 1997/1998 and 1998/1999 seasons due to the A/H3N2 (Sydney) strain epidemics (6,7). Before and after these seasons, i.e., the 1995/1996, 1996/1997, and 1999/2000 season, the surveillance system found that influenza activity remained normal or at a low level (8-10). We evaluated the ISSS during

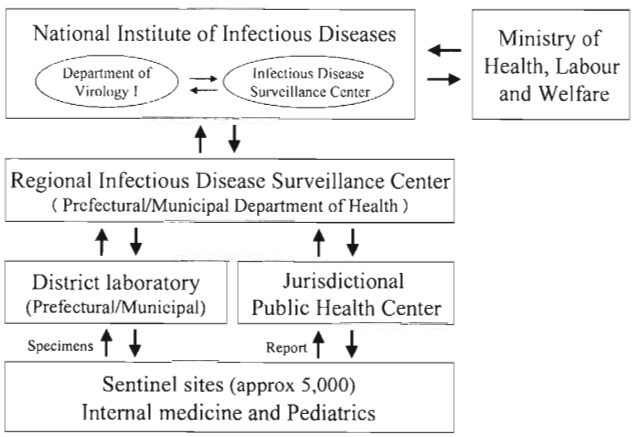

Fig. 1. Microbial and sentinel surveillances for influenza in Japan.

these five consecutive influenza seasons in Kyoto City, Japan.

METHODS

We compared the 1995-2000 data collected by the ISSS with those by the Microbial Isolation Surveillance System (MISS). We reviewed the clinical information regarding patients with ILI, who submitted throat swab specimens during November through March of the next year, and we attempted isolation of the major responsible respiratory pathogens, including influenza virus. In addition, patients who were diagnosed with other respiratory illnesses (e.g., tonsillitis, upper respiratory infections, bronchitis, etc.) and viral gastroenteritises (e.g., viral gastroenteritis of adult, acute vomiting and diarrhea of infancy and childhood), which can be included among the influenza surveillance data (11), were selected for isolation of influenza viruses and other microbial pathogens. In Kyoto City, throat swab specimens from patients with ILI were centrifuged with 3 ml of the Eagle's minimal essential medium (MEM) and filtrated with millipore filters (diameter, 0.45 μm). Then, samples were inoculated on Madin-Darby canine kidney (MDCK) cells. When a cytopathic effect was observed, the type of influenza virus was identified using anti-ferret sera that is provided every preseason by the National Institute of Infectious Diseases. For other virus isolations, FL cells (human amniotic membrane), RD-18S cells (human fetus striated muscle), and Vero cells (African maccaka monkey kidney) were employed. Filtered specimens of these cell types were inoculated in the ddY strain mouse (1-2 days of age) brain or injected hypocutaneously. When the viruses were recovered, they were identified either by a neutralization test, a complement fixation reaction, a hemagglutination inhibition reaction, or a fluorescent antibody technique. In those cases that had developed symptoms of viral gastroenteritis, stool or vomitus specimens were tested for rotavirus and enteric adenovirus (types 40, 41) antigens by enzyme immunoassay. Cytomegalovirus was recovered from urine specimens and identified by gene fragment detection using polymerase chain reaction.

RESULTS

Isolation of pathogens from ILI patients: A total of 676 throat swab specimens together with the associated clinical information were submitted to the Division of Microbiology, Kyoto City Institute of Health and Environmental Sciences. Specimens were gathered by ISSS from patients with ILI (349 specimens) and other illnesses. Influenza viruses were isolated in 161 specimens out of 676. Table 1 displays a comparison of the number of influenza virus isolates and other pathogens recovered from ILI patients by the MISS. Influenza viruses were identified in 144 of 349 specimens; 41 specimens tested positive for influenza A (H1N1) virus, 72 for influenza A (H3N2) virus, and 31 for influenza B virus. Fifty-two other pathogens were identified in 41 specimens (2 pathogens were isolated in 11 of the 41); 8 adenovirus, 3 respiratory syncytial (RS) virus, 3 coxsackievirus, 1 parainfluenza virus, 9 *Staphylococcus aureus*, 3 *Streptococcus pneumoniae*, and 25 other pathogens were also present, including an unidentified pathogen. No pathogens were identified in 164 of the specimens. The number of microbiologically identified influenza

Table 1. Isolation of pathogens from throat swab specimens of patients diagnosed with ILI from November to March in 1995/1996 - 1999/2000 in Kyoto City

(n = 349)

Pathogen	Number of specimen (%)
influenza A/H1N1	41 (11.7)
influenza A/H3N2	72 (20.6)
influenza B	31 (8.9)
adenovirus	8 (2.3)
respiratory syncytial virus	3 (0.9)
coxsackievirus	3 (0.9)
parainfluenza virus	1 (0.3)
herpesvirus	1 (0.3)
echovirus	1 (0.3)
unidentified	1 (0.3)
Staphylococcus aureus	9 (2.6)
Streptococcus pneumoniae	3 (0.9)
Streptococcus type A	15 (4.3)
Streptococcus type B	3 (0.9)
Streptococcus type G	2 (0.6)
Pseudomonas aeruginosa	1 (0.3)
Haemophilus influenzae	1 (0.3)
negative	164 (47.0)

The total number of results exceeds 349 because two pathogens were isolated in 11 of the 349 specimens.
%: 349 = denominator

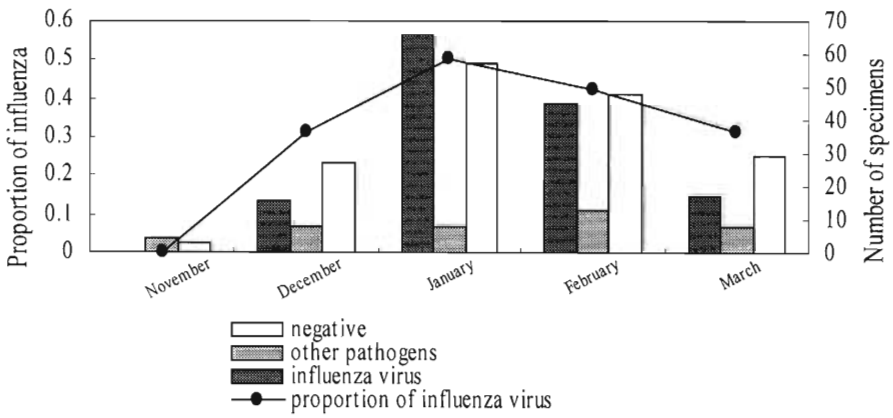

Fig. 2. Results of microbial isolation from patients diagnosed with ILI from November to March in 1995/1996 - 1999/2000 in Kyoto City (n = 349).

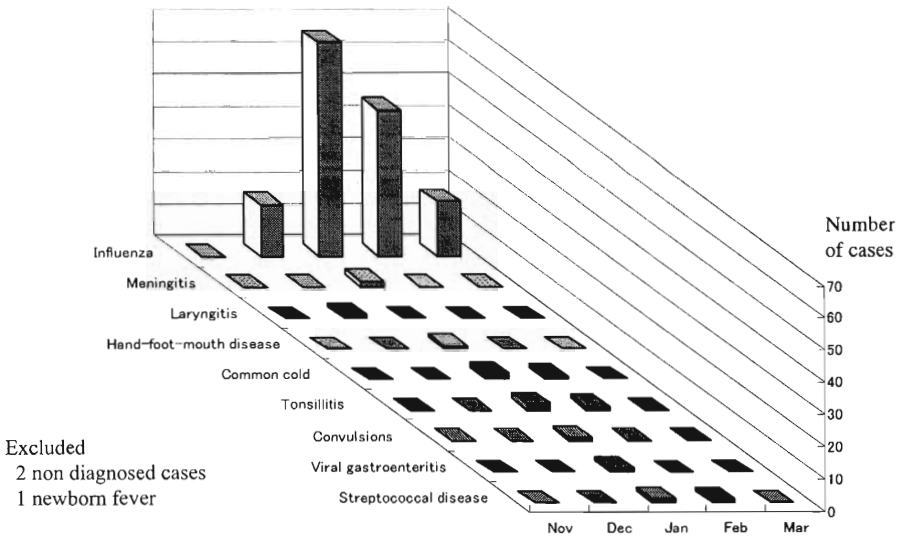

Fig. 3. Clinical diagnosis and number of specimens confirmed as influenza virus by month from November to March in 1995/1996 - 1999/2000 in Kyoto City (n = 161).

cases ranged from 0 to 66, and the number of cases from which other pathogens were isolated ranged from 4 to 13. The number of negative cases ranged from 3 to 57, according to the month (Fig. 2). Figure 3 shows the clinical diagnoses among the cases in which influenza was confirmed. Although there were misdiagnosed cases, e.g., tonsillitis and meningitis, 89.4% (144/161) of the cases were diagnosed correctly. No specific association was observed between types of pathogen and the month in which pathogens were recovered.

Sensitivity, specificity, and predictive value positive (PVP): Regardless of clinical diagnosis, the results of all throat swab specimens used for isolation of the influenza virus during the period of observation were summarized with the goal of evaluating the accuracy of the physicians' clinical diagnosis for influenza; tested values included sensitivity, specificity, and PVP by season and by month, shown in Table 2. In this context, sensitivity indicates the percentage of specimens with a diagnosis of ILI among those submitted by sentinel doctors; among those specimens were ones from which influenza viruses were isolated together with clinical diagnosis. Specificity indicates the percentage of specimens from the total in which influenza virus was not isolated; among these specimens were those for which any diagnosis other than ILI had been made, and for which isolation of the influenza virus was tested; these samples were also submitted by sentinel doctors. PVP indicates the percentage of specimens in which influenza viruses were isolated; among these latter specimens, also submitted by sentinel doctors, were those with a diagnosis of ILI. Sensitivity ranged from 79.1 to 96.8%, specificity ranged from 55 to 76.8%, and PVP ranged from 28.9 to 52.1% by season ($P < 0.001$). On the other hand, sensitivity ranged from 85.7 to 100%, specificity ranged from 38.4 to 92.5%, and PVP ranged from 31.4 to 50.4% by month ($P < 0.001$). Sensitivity and PVP were not calculated for any time period

Table 2. Sensitivity, specificity, and predictive value positive (PVP) for the physicians' clinical diagnosis of influenza from November to March in 1995/1996 - 1999/2000 in Kyoto City

Observation period	Sensitivity (%)	Specificity (%)	PVP (%)
November to March in 1995/1996 season	18/21 (85.7)	32/49 (65.3)	18/35 (51.4)
November to March in 1996/1997 season	9/10 (90.0)	53/69 (76.8)	9/25 (36.0)
November to March in 1997/1998 season	22/24 (91.7)	66/120 (55.0)	22/76 (28.9)
November to March in 1998/1999 season	61/63 (96.8)	76/132 (57.6)	61/117 (52.1)
November to March in 1999/2000 season	34/43 (79.1)	83/145 (57.2)	34/96 (35.4)
All November in 1995-1999	0/0 (–)	86/93 (92.5)	0/7 (–)
All December in 1995-1999	16/18 (88.9)	63/98 (64.3)	16/51 (31.4)
All January in 1996-2000	66/77 (85.7)	50/115 (43.5)	66/131 (50.4)
All February in 1996-2000	45/49 (91.8)	38/99 (38.4)	45/106 (42.5)
All March in 1996-2000	17/17 (100.0)	73/110 (66.4)	17/54 (31.5)
All periods	144/161 (89.4)	310/515 (60.2)	144/349 (41.3)

$P < 0.001$

Sensitivity: Sentinal doctors submitted this number of specimens with the diagnosis of ILI; among these were specimens associated with any clinical diagnosis that had also been tested positive for influenza viruses.
Specificity: The number of specimens in which the influenza virus was not isolated; among these specimens submitted by sentinel doctors were those with any diagnoses other than ILI but which had undergone testing for isolation of the influenza virus.
PVP: The number of specimens in which influenza viruses were isolated; among these specimens submitted by sentinel doctors were those with a diagnosis of ILI.

Table 3. The number of specimens that tested positive for influenza virus and other pathogens, taken from patients diagnosed with viral gastroenteritis from November to March in 1995/1996 - 1999/2000 in Kyoto City

		1995-1996					1996-1997					1997-1998					1998-1999					1999-2000					total
		Nov	Dec	Jan	Feb	Mar	Nov	Dec	Jan	Feb	Mar	Nov	Dec	Jan	Feb	Mar	Nov	Dec	Jan	Feb	Mar	Nov	Dec	Jan	Feb	Mar	
Number of reported cases as s/o viral gastroenteritis*		4	6	1	4	4	0	0	0	2	7	6	1	0	3	7	4	7	3	5	4	3	2	3	1	2	79
among above*, with swab specimens**		2	4	0	0	3	0	0	0	2	5	2	1	0	1	4	1	5	1	4	3	0	1	1	1	2	43
among above**, positive for influenza virus		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	1
Other pathogens	echovirus	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
	S. haemolyticus typeA	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	1	0	1	0	0	0	0	0	0	3
	adenovirus	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	2

in November.

Of 43 throat swab specimens from patients who were clinically diagnosed with viral gastroenteritis, one (2.3%) was virologically confirmed as influenza virus (Table 3).

DISCUSSION

In most industrialized countries, the national infectious disease surveillance authority usually monitors influenza activity by routine reporting from designated sentinel sites. In order to maintain high efficacy of observation, it is crucial to regularly evaluate such sentinel surveillance systems. This is the first evaluation of an ISSS in Kyoto City, Japan.

We found high sensitivity throughout the study period, which supported the efficacy of the present influenza observation system. However, the series of procedures required for isolation testing is tedious, thus posing a major limitation to the practice of confirming influenza in all patients with ILI.

Specificity varied by season, indicating the difficulty of achieving a clinical differential diagnosis of other respiratory illnesses. However, some patients were shown to have some form of viral gastroenteritis (e.g., Norwalk virus infection), these cases were excluded from the influenza case. High viral gastroenteritis activity was observed in the 1999/2000 season (available on website, http://idsc.nih.go.jp/kanja/weeklygraph/gastro.html) (12), and the MISS demonstrated better results in that regard. These findings suggest that a mix of viral gastroenteritis and influenza in an influenza surveillance system would not be a serious problem as imagined.

PVP varied by season, and when calculated by month, PVP peaked in January. The result may be explained that the number of true influenza patients increases rapidly at times when influenza activity is high (i.e., December-February). Improvement of PVP is essential for the early detection of the rise and fall of influenza activity. Since the 2000/2001 season, rapid influenza diagnosis kits detecting influenza A and B viruses have been commercially available, and therefore, PVP should be improved throughout the influenza season.

The well-evaluated ISSS data are useful for improving public health systems. The ISSS is thus a good surveillance system, and further monitoring to strengthen the ISSS will contribute to an improved understanding of the epidemiology of influenza in the community of Kyoto City.

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