Assessment of secondary attack rate and effectiveness of antiviral prophylaxis among household contacts in an influenza A(H1N1)v outbreak in Kobe, Japan, May–June 2009

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This report describes the assessment of the secondary attack rate (SAR) and the effectiveness of post-exposure antiviral prophylaxis among household contacts in the first domestic outbreak of a novel influenza A(H1N1)v between mid-May and early June 2009 in Kobe city, Japan. Of the 293 subjects, 14 (4.8%) household contacts met the case definition and most secondary cases were probably infected around the time of symptom onset date of the respective index case. The SAR among household contacts who did not receive prophylaxis was 7.6%, similar to the rate of seasonal influenza, and the attack rate in siblings was significantly higher than that in parents. We conclude that it is important to establish routine infection control measures for households in order to prevent the spread of the virus among household contacts and, possibly, to the community. We could not conclude whether antiviral prophylaxis was effective or not. However, among close contacts with underlying disease who received prophylaxis, nobody developed a severe form of the disease.

Introduction

Between 16 May and 5 June 2009, 110 laboratory-confirmed cases of influenza A(H1N1)v, affecting mainly high school students, were reported from the Public Health Centre of Kobe City (PHCKC), Japan. The PHCKC provided post-exposure antiviral prophylaxis (oseltamivir or zanamivir) primarily to household contacts with underlying disease, in addition to implementing aggressive school closure throughout the city for one or two weeks from 16 May. The number of new laboratory-confirmed cases decreased in late May following the school closures [1], and community transmission was limited. No severe cases were reported during this period. We suppose that preventing the spread of influenza among household contacts effectively prevented the development of severe disease in each household and the transmission to the community. In this study, we assess the secondary attack rate (SAR) among household contacts who did not receive antiviral prophylaxis and the effectiveness of post-exposure antiviral prophylaxis in preventing the spread of influenza A(H1N1)v among household contacts in this particular outbreak.

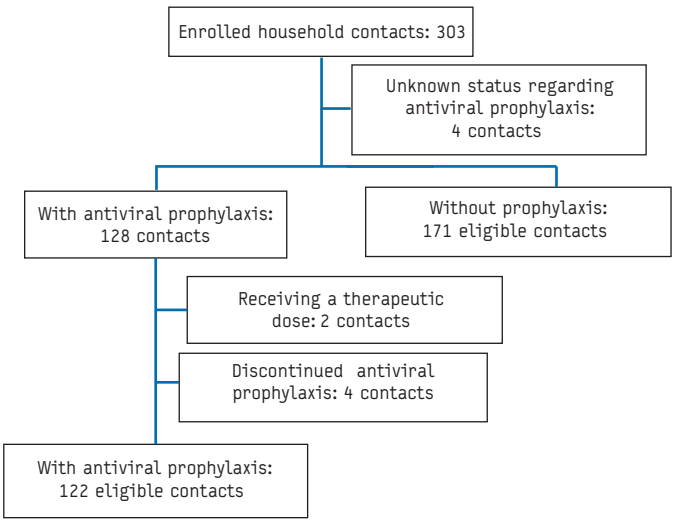
Methods

Subjects and case definition

We included 303 household contacts from 97 households with the exception of three households with one person living alone. The median number of household members including index cases was four, ranging from two to eight. We defined an index case (IC) as the first person in each household who met the case definition described below according to the epidemiological investigation. The PHCKC followed up on these household contacts every day for approximately eight days either from the date when the ICs started antiviral therapy or from the date the PHCKC began to observe household contacts in case the ICs did not take antiviral therapy. In addition, household contacts were requested to stay

Figure 1

Flow diagram of enrolled household contacts, pandemic H1N1 influenza outbreak, Japan, May-June 2009



home but to avoid close contact with the patient in their household during the follow-up period. Household members with influenza-like symptoms were instructed to wear face masks. Along with the PHCKC, we collected data on the symptoms and the use of antiviral prophylaxis. We excluded four contacts for whom information about antiviral prophylaxis was not available, four contacts who had discontinued antiviral prophylaxis and two contacts who were receiving a therapeutic dose (oseltamivir, 150 mg/day, or zanamivir, 20 mg/day; for five days). Overall, our study subjects comprised 122 household contacts receiving and 171 not receiving antiviral prophylaxis (Figure 1)..

Cases were confirmed by using the following case definition for household contacts, which is similar to the definition established by the Ministry of Health, Labour and Welfare at that time [1]:

Suspected case: a person who displayed high fever of ≥38 °C or at least two acute respiratory symptoms (nasal obstruction/

Table 1

Demographic data for index cases, pandemic H1N1 influenza outbreak, Japan, May-June 2009 (n=97)

Total no. of index cases		**97**
Sex	Women, no. (%)	40(41)
	Men, no. (%)	57(59)
Age, median (range)		17(1-53)
<20 years-old, no. (%)		87(90)
Cases with antiviral medication, no. (%)		89(92)
Interval from symptom onset to treatment, median days (range)		1(0-7)

Table 2

Demographic data for household contacts, pandemic H1N1 influenza outbreak, Japan, May-June 2009 (n=293)

		Without prophylaxis	With prophylaxis			
			Total	Oseltamivir	Zanamivir	P-value*
Total no. of subjects		**171**	**122**	**100**	**22**	
Sex	Women, no. (%)	80(47)	65(53)	53(53)	12(55)	P=0.33**
	Men, no. (%)	91(53)	57(47)	47(47)	10(45)	
Age, median (range)		39(0-83)	45 (2-85)	48 (2-85)	14(7-41)	P<0.05***
Age unknown, no.		14	8	8	0	
Relationship to index case, no.						
Parent		85	73	71	2	
Sibling		64	31	11	20	
Child		4	3	3	0	
Spouse		2	2	2	0	
Grandparent		11	11	11	0	
Other		5	2	2	0	
Underlying disease, no.		n=167	n=122			
Asthma		0	9	7	2	
Hypertension		0	13	13	0	
Cardiovascular disease		1	2	2	0	
Diabetes		0	2	2	0	
Neoplasm		0	1	1	0	
Rheumatism		0	4	4	0	
Total		1	31	29	2	P<0.01**
The interval from symptom onset of index cases to prophylaxis, median day (range)			4 (0-8)	4(1-8)	3.5(0-8)	
0			3	0	3	
1			7	7	0	
2			21	19	2	
3			27	21	6	
4			23	20	3	
5			17	13	4	
6			3	2	1	
7			12	10	2	
8			9	8	1	

* Comparing total household contacts receiving prophylaxis to those not receiving prophylaxis
** Chi-square test
*** Wilcoxon rank-sum test

rhinorrhoea, sore throat, cough, fever of ≥37 °C), excluding individuals with negative RT-PCR for influenza A(H1N1)v virus;

Confirmed case: a suspected case with laboratory-confirmed influenza A(H1N1)v infection as tested by RT-PCR.

TABLE 3

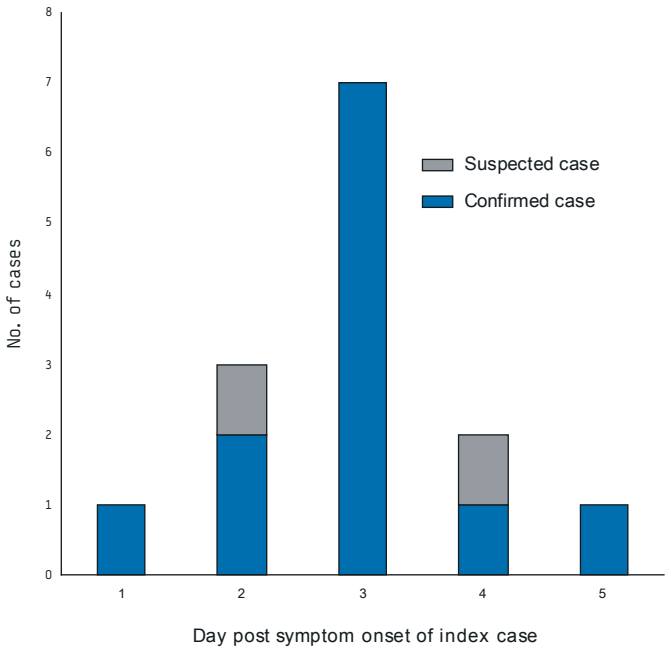
Demographic data for confirmed and suspected cases, pandemic H1N1 influenza outbreak, Japan, May-June 2009 (n=14)

		Confirmed case	Suspected case	Total
No. of cases		**12**	**2***	**14**
Sex	Women, No. (%)	7 (58)	1*(50)	8 (57)
	Men, No. (%)	5 (42)*	1(50)	6 (43)
Age, years				
0-9		2	2*	4
10-19		8	0	8
40-49		1	0	1
50-59		1	0	1
Relationship to index case				
Parent		2	0	2
Sibling		10	1*	11
Child		0	1	1
Spouse		0	0	0
Grandparent		0	0	0
Other		0	0	0
Underlying disease		0	0	0

* Including one case who received antiviral prophylaxis

FIGURE 2

The interval from symptom onset of index cases to symptom onset of household contacts, pandemic H1N1 influenza outbreak, Japan, May-June 2009 (n=14)



Antiviral prophylaxis

Either oseltamivir (75 mg/day for adults or 2mg/kg/day for children*) or zanamivir (10 mg (two inhalers)/day) was administered household contacts for a period of 7–10 days, provided that they had underlying diseases (e.g. asthma or diabetes).

Statistical analyses

We calculated the secondary attack rate (SAR) among household contacts who did not receive antiviral prophylaxis. We also compared the attack rate among siblings and parents who did not receive antiviral prophylaxis in households where the ICs were under 20 years-old. We further compared the attack rate among household contacts receiving and not receiving antiviral prophylaxis to assess its effectiveness. Inter-group comparisons were made using Chi-square test or Fisher's exact test.

Results

Of the 97 ICs, 89 (92%) were treated with antiviral medication (Table 1) and 80 (82%) ICs began antiviral therapy within two days of symptom onset (e.g. nasal obstruction/rhinorrhoea, sore throat, cough or fever of ≥37 °C); 87 (90%) ICs were under 20 years-old.

Zanamivir was prescribed particularly to household contacts in their teens (Table 2), because there are concerns about the association between oseltamivir and abnormal behaviour in this age group in Japan [2].

The gender distribution of household contacts was not significantly different between the groups receiving and not receiving antiviral prophylaxis. However, the household contacts receiving prophylaxis were significantly older (P<0.05, Table 2).

Of the 293 subjects, 14 (4.8%) in 13 households (representing 13 ICs) met the case definition: 12 confirmed cases (4.1%) and two suspected cases (0.7%) (Table 3). All 13 ICs took antiviral medication within two days of symptom onset. The median interval from symptom onset of ICs to symptom onset of the 14 contacts was three days (range: 1–5 days; Figure 2).

Only one suspected case (female, under five years old) had a history of receiving prophylaxis during this outbreak. The interval from symptom onset of her IC to the administration of antiviral prophylaxis was two days. The SAR in household contacts who did not receive antiviral prophylaxis was 7.6% (13/171)*.

In those households in which the ICs were under 20 years-old, 10 (16.4%)* cases in siblings and two (2.4%)* cases in parents met the case definition. The attack rate in siblings was significantly higher than that in parents. The odds ratio (OR) was 7.84 (95% confidence interval (CI): 1.52–54.2; Table 4).

The difference in the attack rate between household contacts who had received prophylaxis and those who had not was statistically significant. However, the household contacts receiving prophylaxis were significantly older, so we stratified household contacts according to age (≥20 years-old or <20 years-old). After that, there was no statistical significance in either group (Table 5).

Discussion

The United States Centers for Disease Control and Prevention (US CDC) have estimated that the incubation period of influenza A(H1N1)v could be between one and seven days, but more likely

between one and four days [3]. Our investigation showed that the median interval from symptom onset of ICs to symptom onset among the 14 cases in the household contacts was three days (range: 1–5 days). These results indicate that most secondary cases were probably infected around the time of symptom onset of the ICs. Therefore, routine infection control measures for each household should be established because it is sometimes difficult for public health authorities to intervene in affected households immediately after ICs develop symptoms.

The World Health Organization (WHO) reported that the current estimate of the SAR of influenza A(H1N1)v was 22–33%, and the SAR of seasonal influenza was 5–15% [4]. Our investigation showed a SAR of 7.6%. This rate was lower than that for influenza A (H1N1) v reported by WHO and similar to the rate of seasonal influenza. The PHCKC and the mass media actively provided information to the public about influenza A(H1N1)v and emphasised the importance of infection control measures (such as hand washing, cough etiquette including wearing masks) at home during the outbreak period. These measures or social pressure might have been effective in reducing the number of secondary cases.

We could not conduct sero-epidemiological examinations in this investigation. Therefore, mild or asymptomatic cases that did not meet the case definition were possibly overlooked, and the SAR may have been underestimated. This issue requires further investigation.

The attack rate among siblings was significantly higher than the attack rate for parents, indicating greater contact between siblings or that infection control measures might not have been satisfactorily practiced by the younger household contacts. We conclude that it is necessary to effectively convey infection control advice among young household members, as well as to their parents, to prevent the virus from spreading in the household and, possibly, to the community. Both the public health sector and the mass media can play an important role in this responsibility..

Antiviral prophylaxis for seasonal influenza among household contacts has been shown to be effective [5–8]. Our data indicated no significant difference in the SAR in households stratified by age and age was considered to be a confounding factor. However, only one contact who had received antiviral prophylaxis met the case definition, so it was impossible to conclude whether antiviral prophylaxis was effective or not. Moreover, because no severe cases were reported among these households, we think that post-exposure antiviral prophylaxis can be given to close contacts at high risk for developing influenza complications, as recommended by the European Centre for Disease Prevention and Control (ECDC) and the US CDC [9,10]. The effectiveness of antiviral prophylaxis warrants further study and discussion, regarding its potential to prevent severe cases and the cost-benefit relationship.

Conclusion

From the results of this study, we conclude that it is important to establish routine infection control measures for households in order to prevent the spread of the virus among household contacts and, possibly, to the community. In future outbreaks, educating young household contacts on infection control measures through public notification and the media may be effective in controlling the outbreak. The effectiveness of prophylaxis for household contacts was not determined. However, close contacts with underlying disease who received prophylaxis did not develop a severe form of the disease.

Table 4

Comparison between the secondary attack rate in siblings and parents, pandemic H1N1 influenza outbreak, Japan, May-June 2009 (n=143)

	Cases	Not cases	Total	OR(95%CI)	P-value
Siblings	10	51	61	7.84	<0.01*
Parents	2	80	82	(1.52-54.2)	
Total	12	131	143		

CI: confidence interval; OR: odds ratio.
*Chi-square test

Table 5

Comparison between household contacts receiving antiviral prophylaxis and those not, pandemic H1N1 influenza outbreak, Japan, May-June 2009 (n=293)

	Cases	Not cases	Total	OR(95%CI)	P-value
With prophylaxis	1	121	122	0.10	<0.05*
Without prophylaxis	13	158	171	(0-0.75)	
Total	14	279***	293		
With prophylaxis < 20 years-old	1	23	24	0.15	0.09**
Without prophylaxis < 20 years-old	11	39	50	(0.01-1.30)	
Total	12	62	74		
With prophylaxis ≥ 20 years-old	0	90	90	0	0.50**
Without prophylaxis ≥ 20 years-old	2	105	107	(0-4.86)	
Total	2	195	197		

CI: confidence interval; OR: odds ratio.
* Chi-square test
** Fisher's exact test
*** Including 14 without prophylaxis and eight with prophylaxis for whom the age was not known.

Acknowledgements

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*Authors' correction: On request of the authors, the two percentages in this sentence were corrected on 4 September 2009. Further, the sentence "The SAR in household contacts was 7.6%." was changed to read "The SAR in household contacts who did not receive antiviral prophylaxis was 7.6% (13/171)" on 7 September 2009 on request of the authors, information on oseltamivir dosage was added ("75 mg/day for adults or 2mg/kg/day for children"), and the percentage of confirmed male cases in Table 3 was corrected to read 5(42).

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