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The Dominant Antigenic Group of Influenza C Infections Changed from C/Sao Paulo/378/82-Lineage to C/Kanagawa/1/76-Lineage in Yamagata, Japan, in 2014

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Influenza C virus is ubiquitous and usually causes a mild upper respiratory tract illness in children and lower respiratory tract illnesses such as bronchitis and pneumonia in infants and children (1,2). To clarify the epidemiology of acute viral respiratory infections in children in Yamagata, Japan, as a part of the National Epidemiological Surveillance of Infectious Diseases, Japan based on the Infectious Diseases Control Law, we performed virus isolation using HHVM, HHVMRG, and HHV6MRG microplates, containing HEF, HEp-2, Vero or VeroE6, MDCK, RD-18S, and GMK cell lines as well as the HMV-II cell line, in part, for the isolation of viruses, including influenza virus C (1,3–7). In particular, for the isolation of influenza virus C, we obtained nasopharyngeal specimens from persons who visited one of two pediatric outpatient clinics in Yamagata city or Yamanobe town in Yamagata Prefecture, as described previously (7). Of the 6 distinct virus groups (C/Taylor/1233/47-lineage, C/Kanagawa/1/76-lineage, C/Mississippi/80-lineage, C/Yamagata/26/81-lineage, C/Aichi/1/81-lineage, and C/Sao Paulo/378/82-lineage) categorized on the basis of antigenic analysis by the hemagglutination-inhibition test using monoclonal antibodies against the hemagglutinin-esterase (HE) glycoprotein (7,8), all except the C/Taylor/1233/47-lineage have been detected in Yamagata. The viruses belonging to the C/Aichi/1/81-lineage and C/Yamagata/26/81-lineage co-circulated in Yamagata between 1988 and 1992 (9,10). Then, strains of the C/Yamagata/26/81-lineage, C/Kanagawa/1/76-lineage, and C/Sao Paulo/378/82-lineage were dominantly isolated in Yamagata, between 1996 and 2000, between 2002 and 2004, and between 2006 and 2012, respectively (7). The strains of the C/Mississippi/80-lineage were sporadically isolated in Yamagata in 1992, 2000, and 2004 (7,10). Our recent longitudinal epidemiological studies, in particular, have revealed that epidemics of influenza virus C infections periodically

occur from winter to early summer in even-numbered years, with 1–4 virus groups (mostly 1 or 2 groups) circulating one after the other or simultaneously (7). Between 2008 and 2010, all 55 isolates belonged to the C/Sao Paulo/378/82-lineage (Fig. 1), which first appeared in 2004 (7). In 2012, we isolated not only 23 C/Sao Paulo/378/82-lineage strains but also 6 C/Kanagawa/1/76-lineage strains (Fig. 1), which had not been detected since 2006 (7). We herein report our findings regarding the latest epidemic in 2014.

We isolated 21 strains between May and August 2014 (Fig. 1). Antigenic analysis by the hemagglutination-inhibition test using anti-HE monoclonal antibodies demonstrated that 2 lineages (13 C/Kanagawa/1/76-lineage and 8 C/Sao Paulo/378/82-lineage strains) were simultaneously in circulation (Table 1). We also noticed that the dominant group changed from the C/Sao Paulo/378/82-lineage to C/Kanagawa/1/76-lineage in 2014 (Fig. 1). Such replacement of the dominant group has been observed twice previously in Yamagata: the replacement of the C/Yamagata/26/81-lineage by the C/Kanagawa/1/76-lineage in 2002 and of the C/Kanagawa/1/76-lineage by the C/Sao Paulo/378/82-lineage in 2006 (7). Our previous study suggested that antigenic replacement occurred as a result of immune selection within older children and/or adults who have cross-reactive antibodies (7). Therefore, continuous seroepidemiological surveying is important to ascertain the change in the dominant antigenic group.

Further sequence analysis of the HE region revealed that 1 cluster, including C/Yamagata/6/2014 and C/Yamagata/33/2014, branched off from another cluster represented by C/Yamagata/27/2004 within the C/Sao Paulo/378/82-lineage (Fig. 2). Three strains (C/Yamagata/15/2014, C/Yamagata/30/2014, and C/Yamagata/32/2014) were classified into the cluster represented by C/Yamagata/27/2004, together with the C/Sao Paulo/378/82-lineage strains isolated in Yamagata between 2006 and 2012. Interestingly, these 3 strains could be distinguished from the other C/Sao Paulo/378/82-lineage strains by their reactivity with monoclonal antibody J9 (Table 1). This is the first time that 2 distinct clusters within 1 lineage have been observed to be in simultaneous circulation in Yamagata. However, the phylogenetic tree (Fig. 2) suggested that such a phenomenon could occur in other areas of the

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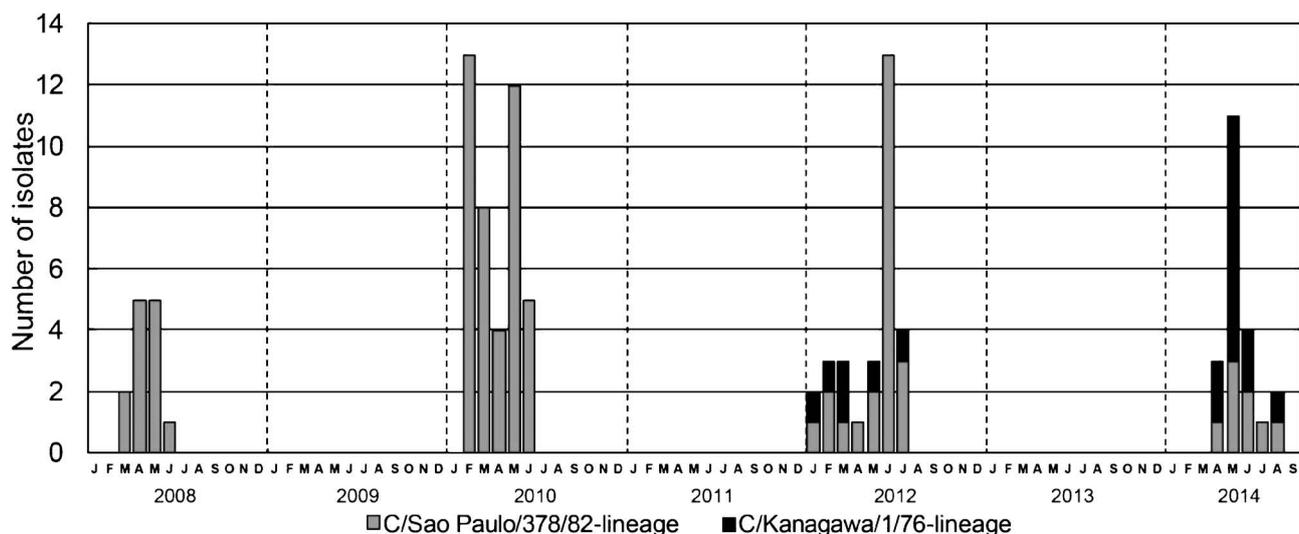


Fig. 1. Monthly distribution and antigenicity of influenza C virus strains isolated in Yamagata, Japan between 2008 and 2014.

Table 1. Antigenic analysis of representative influenza C virus isolates by HI tests with anti-HE monoclonal antibodies (MAbs)

Virus strain	HE lineage	HI titer of anti-HE MAb ¹⁾			
		J9	U4	U9	U1
Reference isolates					
C/Kanagawa/1/76	Kanagawa/76	< ²⁾	40	160	<
C/Sao Paulo/378/82	Sao Paulo/82	20	3,200	128,000	128,000
C/Yamagata/27/2004	Sao Paulo/82	<	1,600	64,000	64,000
C/Yamagata/2/2010	Sao Paulo/82	20	1,600	64,000	128,000
C/Yamagata/29/2012	Sao Paulo/82	<	3,200	64,000	128,000
2014 season isolates					
C/Yamagata/13/2014	Kanagawa/76	<	40	640	<
C/Yamagata/14/2014	Kanagawa/76	<	20	320	<
C/Yamagata/16/2014	Kanagawa/76	<	40	320	<
C/Yamagata/35/2014	Kanagawa/76	<	40	160	<
C/Yamagata/15/2014	Sao Paulo/82	1,280	3,200	16,000	16,000
C/Yamagata/30/2014	Sao Paulo/82	1,280	6,400	64,000	16,000
C/Yamagata/32/2014	Sao Paulo/82	1,280	6,400	64,000	16,000
C/Yamagata/6/2014	Sao Paulo/82	<	1,600	16,000	16,000
C/Yamagata/33/2014	Sao Paulo/82	<	1,600	32,000	32,000

¹⁾: The J9, U4, and U9 MAbs and the U1 MAb are directed against the non-overlapping antigenic sites A-1 and A-3, respectively (8).

²⁾: Titer below 20.

world. In Catalonia, Spain, C/Catalonia/1284/2009, which is similar to C/Yamagata/15/2014, and C/Catalonia/1430/2009, which is similar to C/Yamagata/6/2014, were in co-circulation in 2009 (11).

In conclusion, we observed that the dominant group changed from the C/Sao Paulo/378/82-lineage to the C/Kanagawa/1/76-lineage, and for the first time, we found that 2 different clusters among the C/Sao Paulo/378/82-lineage were in co-circulation in Yamagata, Japan, in 2014. To clarify the longitudinal epidemiology of acute viral respiratory infections in children, it is necessary to continue surveillance and accumulate further data in a local community such as Yamagata.

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Conflict of interest None to declare.

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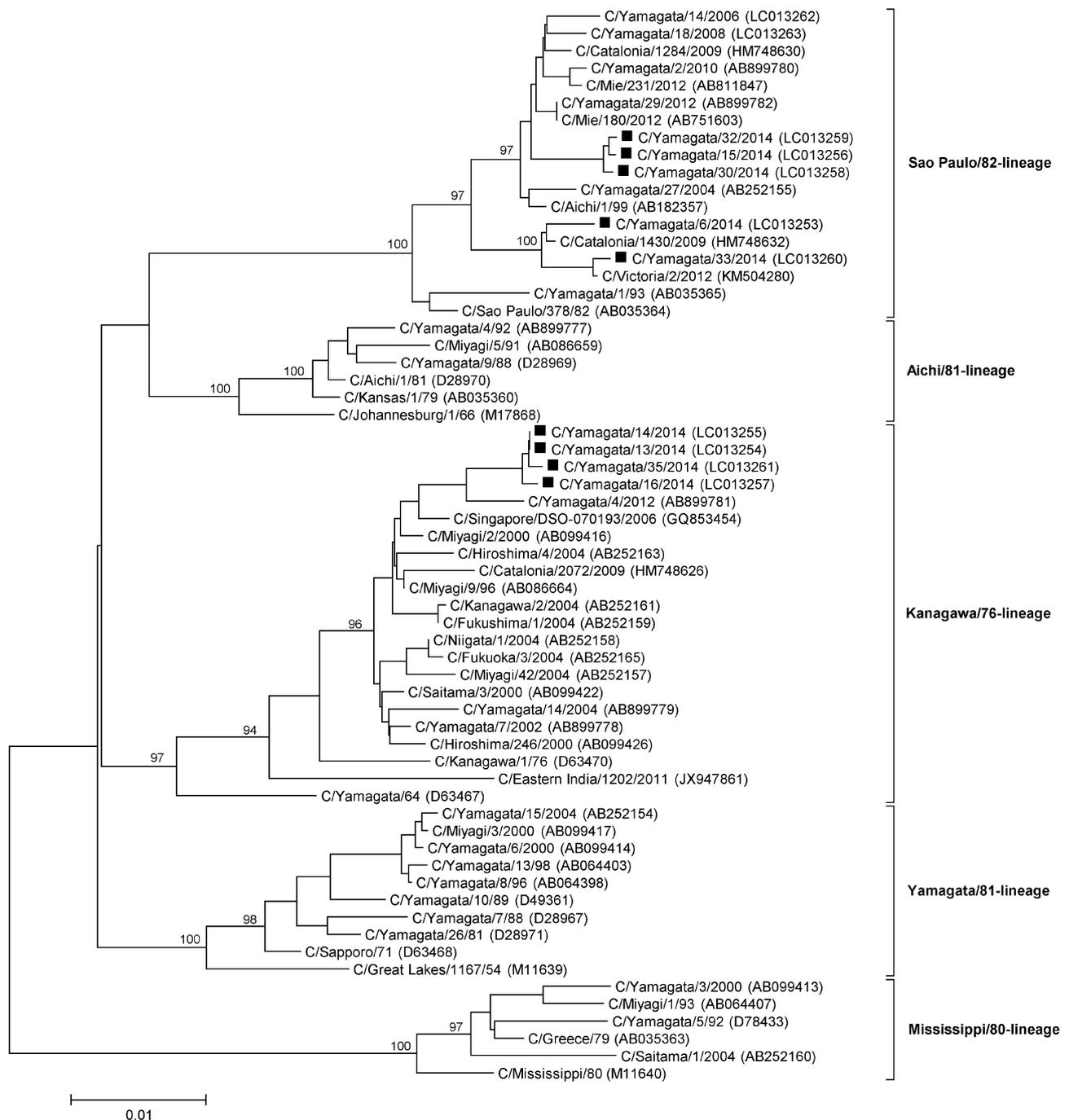


Fig. 2. Phylogenetic tree for the HE gene of influenza C virus isolates in Yamagata, Japan and reference strains. Isolates obtained in Yamagata in 2014 are indicated by squares. GenBank accession numbers are also shown.

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