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An Epidemiological Analysis of Summer Influenza Epidemics in Okinawa

Satoko Sunagawa[1,2], Yoshikazu Iha[1], Katsuya Taira[3], Sho Okano[3], Takeshi Kinjo[1], Futoshi Higa[1], Kazufumi Kuba[4], Masao Tateyama[1], Katsunori Nakamura[2], Shota Nakamura[5], Daisuke Motooka[5], Toshihiro Horii[5], Gretchen L. Parrott[1] and Jiro Fujita[1]

Abstract

Objective This study evaluates the difference between winter influenza and summer influenza in Okinawa.

Methods From January 2007 to June 2014, weekly rapid antigen test (RAT) results performed in four acute care hospitals were collected for the surveillance of regional influenza prevalence in the Naha region of the Okinawa Islands.

Results An antigenic data analysis revealed that multiple H1N1 and H3N2 viruses consistently co-circulate in Okinawa, creating synchronized seasonal patterns and a high genetic diversity of influenza A. Additionally, influenza B viruses play a significant role in summer epidemics, almost every year. To further understand influenza epidemics during the summer in Okinawa, we evaluated the full genome sequences of some representative human influenza A and influenza B viruses isolated in Okinawa. Phylogenetic data analysis also revealed that multiple H1N1 and H3N2 viruses consistently co-circulate in Okinawa.

Conclusion This surveillance revealed a distinct epidemic pattern of seasonal and pandemic influenza in this subtropical region.

Key words: influenza, pandemic, antigen test, subtropical region, epidemiology

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Introduction

The seasonal patterns of human influenza in temperate regions have been well documented; however, the seasonal patterns in tropical and subtropical areas are not as simple or as well pronounced as those in temperate regions around the world. It has been demonstrated that in subtropical areas such as Taiwan, Hong Kong, and Singapore, influenza epidemics are observed throughout the year (1). The Okinawan islands are located in the southernmost part of Japan (latitude 26° N), where the climate is also subtropical.

In Okinawa, several episodes of influenza epidemics occur during the summer season (2-5). This report describes the results of an eight-year surveillance of influenza incidence in the Naha region of Okinawa Island. In addition, to further understand influenza epidemics during the summer in Okinawa, we compared the types of viruses obtained in the winter season with the types of viruses obtained in the summer seasons. Furthermore, full genome sequences of representative human influenza A and influenza B were evaluated to demonstrate the differences between viruses with the same antigenic determinants.

[1]Department of Infectious, Respiratory, and Digestive Medicine, Control and Prevention of Infectious Diseases, Faculty of Medicine, University of the Ryukyus, Japan, [2]Department of Hospital Pharmacy, Faculty of Medicine, University of the Ryukyus, Japan, [3]Department of Biological Science, Okinawa Prefectural Institute of Health and Environment, Japan, [4]Clinical Laboratory Center, The Medical Association of Naha City, Japan and [5]Department of Infection Metagenomics, Research Institute for Microbial Diseases, Osaka University, Japan
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Correspondence to Dr. Jiro Fujita, fujita@med.u-ryukyu.ac.jp

Materials and Methods

Study population and influenza antigen tests

Patients with influenza-like symptoms visiting one of the four general hospitals within the cities of Naha and Urasoe, Okinawa, between January 2007 and December 2014 were included in this study. Intranasal or throat swab specimens were obtained when influenza was clinically suspected by physicians. Rapid antigen tests (RATs) using the nasal or throat swab samples were then performed to diagnose influenza A or B infection. This diagnostic procedure is part of conventional clinical practice. The RAT results were anonymously collected from the hospitals by the Clinical Laboratory Center of the Medical Association of Naha City, Okinawa. The investigation period included the H1N1 2009 pandemic (H1N1pdm) in Okinawa.

Virus isolation

Nasopharyngeal specimens from influenza patients were collected at sentinel medical facilities before the initiation of influenza therapy. The samples were kept at 4℃ at the medical facilities and transferred to the microbiology division of the Okinawa Prefectural Institute of Health and Environment for influenza virus isolation and growth. After viral culture, supernatants (200 μL) of nasopharyngeal swabs were inoculated into Madin-Darby canine kidney (MDCK) cells, with 1 mL of maintenance medium, containing trypsin at a concentration of 5.0 μg/mL, per well in 24-well plates. The plates were incubated at 35℃ in a 5% CO_2 atmosphere for 1 week to assess the cytopathic effects. All of the isolates were typed and subtyped by the hemagglutination inhibition assay.

Genomic analysis

RNA extraction

The analyzed samples were unlinked and anonymous in the Osaka Prefectural Institute of Public Health. This study was approved by the ethics review committee of both the Osaka Prefectural Institute of Public Health and Osaka University. Viruses were propagated in MDCK cells. The supernatants were suspended in TRIzol LS Reagent (Life Technologies, Carlsbad, CA, USA) for 60 minutes. Total RNA was extracted using a PureLink™ RNA Mini Kit (Life Technologies) in accordance with the manufacturer's instructions. Contaminating DNA was eliminated with DNAase I (Life Technologies).

One-step reverse transcription-PCR (RT-PCR)

Total RNA was subjected to One-step RT-PCR using SuperScript III/Platinum Taq HiFi One-step RT-PCR Kit (Life Technologies) to detect the receptor-binding site within the hemagglutinin (HA) molecule. The primers used were as follows: forward primer, 59-416TTGAAAGGTTTGAGATAT TC435-39; reverse primer, 59-784CTAGTGTCCAGTAATAG TTC765-39. RNA was extracted using a QIAamp viral RNA Mini kit (QIAGEN Inc., Valencia, CA, USA). A 140-μL volume of virus suspension from the infected culture or embryonated egg yielded a volume of 60 μL of extracted RNA.

Genomic shotgun sequencing and data analysis

Extracted RNA from the supernatant of MDCK culture was subjected to direct metagenomics shotgun sequencing. The RNA samples were reverse transcribed with Superscript III (Life Technologies) and converted to double-stranded DNA using the Klenow Fragment (New England Biolabs Inc., Ipswich, MA, USA). The resulting DNA was treated with Nextra XT DNA Library Prep Kit (Illumina, San Diego, CA, USA). Genomic shotgun sequencing was performed on MiSeq (Illumina). The sequence reads assigned to influenza viruses were collected and assembled using the CLC genomics work bench software program (QIAGEN Inc.).

Review of literature

We reviewed articles concerning summer influenza through MEDLINE (key words: influenza and summer). Articles not listed in the MEDLINE and those written in languages other than English were excluded.

Results

The number of positive cases of influenza A and B infection identified each week from January 2007 to December 2014 are shown in Fig. 1. From January 2007 to December 2014, samples from 180,752 patients were tested with RATs. During the same time period, 46,192 cases (25.6% of those tested) were positive for influenza virus antigen. Most cases were diagnosed as influenza A (37,994 cases; 21.0%) but some (8,198 cases; 4.5%) were diagnosed as influenza B infection.

From January 2007 to December 2014, peaks were observed in 6 (75%) of the 8 summer seasons. In 2007, influenza was detected in both winter and summer, with the summer outbreak composed of influenza A and B. A small outbreak of influenza B infection also occurred in April 2008. Intense epidemic peaks were also noted in August 2009 and December 2009. These two epidemic peaks were caused by the influenza A/H1N1 2009 pandemic (H1N1 pdm) and therefore appear quite different from typical seasonal influenza epidemics. Following the pandemic, in the summer 2010, influenza was not prominent. In 2011, 2013, and 2014, summer influenza was mainly caused by the influenza B virus. In 2012, summer influenza was again caused by a combination of influenza A and B.

The number of influenza virus isolates recovered in the winter season (50w-8w) and summer season (23w-35w) at the microbiology division of the Okinawa Prefectural Institute of Health and Environment are shown in Table 1. From December 2006 to August 2015, a total of 441 and 776 influenza viruses were collected during winter and summer seasons, respectively. Across all winter seasons, the numbers of influenza A/H1N1, A/H1N1pdm, A/H3N2, and B virus

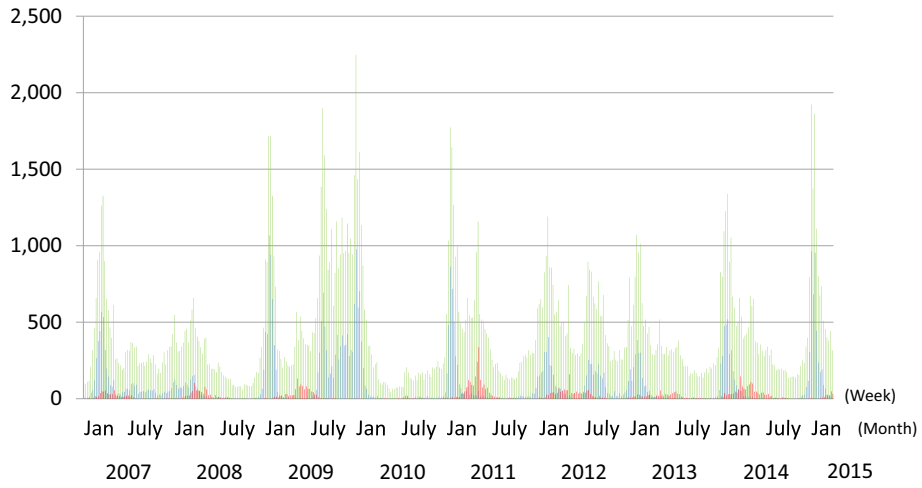

Figure 1. **Incidence of influenza A and B from 2007 to 2014 in four participating hospitals in the Naha region of Okinawa, Japan. Green designates the number of rapid antigen tests performed, blue designates the number of positive results for influenza A virus, and red designates the number of positive results for influenza B.**

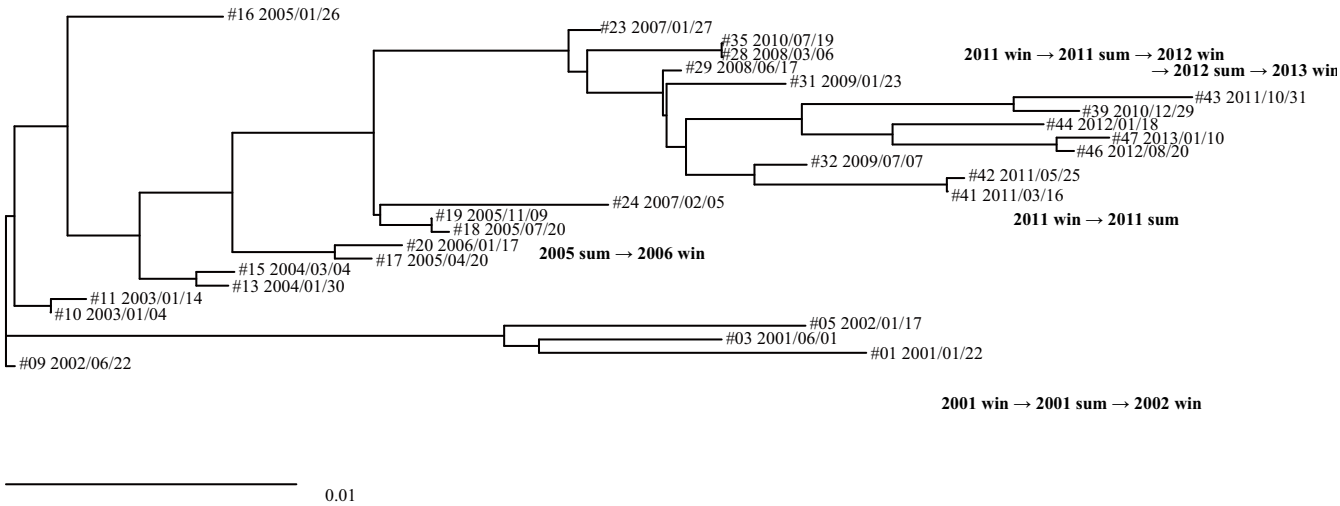

Figure 2. **A genomic analysis of the hemagglutinin gene of A/H3N2 viruses obtained in Okinawa.**

Table 1. **Types of Influenza Virus Cultured in Okinawa.**

	A/H3N2	A/H1N1	A/H1N1pdm	B
(2006)-2007 Winter (50w-8w)	13	0	-	0
2007 Summer (23w-35w)	0	10	-	2
(2007)-2008 Winter (50w-8w)	0	13	-	0
2008 Summer (23w-35w)	5	0	-	6
(2008)-2009 Winter (50w-8w)	11	22	-	2
2009 Summer (23w-35w)	41	0	588	2
(2009)-2010 Winter (50w-8w)	0	0	83	0
2010 Summer (23w-35w)	6	0	6	9
(2010)-2011 Winter (50w-8w)	12	0	105	0
2011 Summer (23w-35w)	7	0	0	17
(2011)-2012 Winter (50w-8w)	57	0	0	10
2012 Summer (23w-35w)	36	0	0	13
(2012)-2013 Winter (50w-8w)	23	0	0	9
2013 Summer (23w-35w)	0	0	3	7
(2013)-2014 Winter (50w-8w)	38	0	23	5
2014 Summer (23w-35w)	0	0	1	8
(2014)-2015 Winter (50w-8w)	14	0	0	1
2015 Summer (23w-35w)	3	0	0	6
SUM	263	45	809	91

Table 2. Summary of Summer Influenza Reported from Several Countries.

Nation	Virus types	Background	References
Taiwan	A+B	Subtropical city	6
China(Jingzhou)	A+B	Hospitalized adults and adolescents	7
China(Hong Kong)	A+B	Subtropical city	8
Mexico	A(H1N1pdm)	School	9
China(Hong Kong)	A+B	Subtropical city	10
China(Hong Kong)	A+B	Subtropical city	11
China(Shanghai)	A+B	Influenza-like illness	12
15 countries	A(H5N1)	Avian influenza	13
China	A	Childhood viral acute respiratory infections	14
China	Influenza	Respiratroy viruses found in children and adults	15
China(Hong Kong)	Influenza	Elderly patients	16
China	A(H7N9)	Avian influenza	17
England	A+B	Influenza and other respiratory viruses	18
Australia	A(H1N1pdm)	Seroprevalence	19
China	A+B	Subtropical cities	20
Pakistan	A+B	Acute respiratory illness	21
China	A+B	Hospitalization	22
China	A	Childhood viral acute respiratory infections	23
China	A+B	Influenza-like illness	24
Taiwan	A	Moleular epidemiology	25
China	A+B	Geographic divisions	26
137 global locations	A+B	Global map	27
Japan	A(H3N2)+A(H1N1)+B	Epidemic	5
Australia	A(H3N2)+A(H1N1)+B	Epidemic	28
Okinawa	A(H3N2)+A(H1N1pdm)+B	Influenza-like illness	4
Italy	B	Travellers to Italy from Lebanon, Senegal, and Uzbekistan	29
Okinawa	A+B	Epidemic	3
Okinawa	A (H3N2) +A(H1N1) +B	Epidemic	2
France	A(H3N2)	Nursing home	30
Japan	A(H3)+B	Epidemic	31
Vietnam	A(H3N2)+A(H1N1)+B	Epidemic	32
East and Southwest Asia	-	Epidemic	1
Japan	A(H3N2)	Hospital	33
Australia	A(H3N2)	Prison	34
Australia	A(H3N2)	Nursing home	35
United Kingdom	A(H3N2)	Young children	36
USA	A(H3N2)	Tourists in Yukon and Alaska	37
Australia	A	Trans-Tasmanian cruise	38
USA and Canada	A(H3N2)	Cruise ships	39
USA	A(H3N2)	Nursing home	40
Northern Ireland	B	School	41

*related to travel, **epidemic in restricted insititutes

isolates were 35, 211, 168, and 27, respectively. However, across all summer seasons, the number of influenza A/H1N1, A/H1N1pdm, A/H3N2, and B virus isolates were 10, 598, 98, and 70, respectively.

The annual analysis of winter infections showed a combination of A/H1N1 (including A/H1N1pdm), A/H3N2, and B viruses in 2009 and 2014, A/H1N1pdm and A/H3N2 viruses in 2011, and A/H3N2 and B viruses in 2012, 2013, and 2015. However, in 2007 and 2010, only A/H3N2 or A/H1N1pdm, respectively, were circulating in our data population (Table 1). The annual analysis of summer infections showed mixed circulation of A/H1N1 and B viruses in 2007; A/H3N2 and B viruses in 2008, 2011, 2012, and 2015; A/H1N1, A/H3N2, and B viruses in 2009 and 2010; and A/H1N1pdm virus and B viruses in 2013 and 2014 (Table 1).

Based on the evidence demonstrated in Table 1, the virus type in the winter was frequently similar to the previous summer pattern. In addition, influenza viruses cultured during the winter and summer of the same year had antigenic differences, except in 2012. Furthermore, influenza B virus was observed consistently and with a higher incidence in the summer seasons, except for the summer of 2009, where A/H1N1pdm dominated. Interestingly, in 2012, the A/H3N2 virus demonstrated equal incidence during winter and summer.

Genomic analysis (Fig. 2)

This study utilized 28 human A/H3N2 influenza virus isolates. A genomic analysis of the samples derived from the same time period revealed that influenza outbreaks may not contain closely related viruses, in Okinawa. However, A/H3N2 (Jun 17/2008) was more closely related to A/H3N2 (Jan 23/2009) than any other sequence. Additionally, A/H3N2 (Aug 20/2012) more closely resembled A/H3N2 (Jan 10/2013) than any other sequence. Taken together, these

data suggest that even though the antigenic type was the same, the genomic patterns of summer viruses diverge from previous winter viruses and more closely resemble the viruses detected during the following winter seasons.

Review of the literature (Table 2)

There are many reports regarding summer influenza (1-41). Recently, there have been several reports concerning summer influenza from the southern parts of China in multiple climatic environments (7, 8, 10-12, 14-17, 20, 22-24, 26). Summer influenza has also been reported from other subtropical areas such as, Mexico (9), Pakistan (21), Taiwan (6, 25) and Vietnam (32). Epidemics of summer influenza in Japan have been reported in Okinawa (2-5), Hokkaido (31), and Nara (33). In older reports, influenza epidemics in summer were observed primarily as a result of travel (29, 37-39) or as small, contained outbreaks (30, 33-35, 40). Furthermore, in recent articles, it has been demonstrated that summer influenza can be a frequent cause of acute respiratory infections in children and adults (4, 12-16, 18, 21-24).

Discussion

In subtropical areas, it is well-known that influenza pandemics frequently occur in the summer season. In addition, there are several reports concerning summer influenza from the southern parts of China. However, the mechanism behind summer influenza epidemics has not been clarified. As demonstrated in this study, summer epidemics of influenza were frequently observed in the subtropical area of Okinawa, Japan. Furthermore, it has been demonstrated that summer influenza was one of the main causes of acute respiratory infections in children and adults in summer seasons (4, 12-16, 18, 21-24), especially in subtropical areas. Influenza B viruses have been proven to play an important role in summer epidemics and therefore more research should be devoted to determining the molecular correlates or environmental factors causing summer respiratory infections.

Our data also show that the types of influenza viruses obtained in winter are different from those obtained during the summer. A genomic analysis showed that the H3N2 viruses obtained in winter season were genetically different from those cultured in summer. The observed genomic patterns further suggest that summer viruses diverge from the previous winter viruses and more closely resemble the viruses detected in the following winter seasons, providing further proof that subtropical areas of Asia are an important breeding ground for emerging influenza strains.

The impact of the H1N1 2009 pandemic on subtropical and tropical regions is of interest. In the summer of 2009, a new influenza virus produced a significant pandemic in Okinawa. This evidence supports the idea when new and more virulent viruses emerge, significant epidemics can result, regardless of the season.

The data shown in Table 2 indicate that summer influenza has been reported quite frequently recently, especially in subtropical cities. In previous reports, epidemics were found to be related to travel (29, 37-39) or occurred in restricted institutions (30, 31, 34, 35, 40). However, recently, epidemics of the H5N1 avian influenza (13), H7N9 avian influenza (17), and A/H1N1pdm (4, 9, 19) have been reported. Very recently, Hsieh et al. reported on virus types circulating in Taiwan (6). In addition, Zheng et al. reported virus types circulating in Jingzhou, China (7). Surprisingly, the virus types detected in Okinawa are very closely related to those detected in Taiwan (6) and Hong Kong (11) but not in Jingzhou, China (7) or in Pakistan (21), suggesting that the viruses detected in Okinawa might be derived from Taiwan or Hong Kong, or vice-versa.

In conclusion, antigenic and phylogenetic data analyses revealed that influenza viruses consistently co-circulate in Okinawa, causing both summer and winter epidemics. More research is needed to determine the molecular components that cause virulence on a pandemic scale. Our analysis showed that new phylogenetic lineages and antigenic variants emerging in summer were likely to be the progenitors of the epidemic strains during the following traditional winter flu season. Okinawan flu samples might provide important clues for predicting which strains of influenza virus will spread globally.

The authors state that they have no Conflict of Interest (COI).

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