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Comparative epidemiology of influenza A and B viral infection in a subtropical region: a 7-year surveillance in Okinawa, Japan

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Research article

2 Comparative epidemiology of influenza A and B viral infection in a subtropical region:
A 7-year surveillance in Okinawa, Japan

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Abstract

26 *Background*

28 The epidemic patterns of influenza B infection and their association with climate
conditions are not well understood. Influenza surveillance in Okinawa is important for
clarifying transmission patterns in both temperate and tropical regions. Using
30 surveillance data, collected over 7 years in the subtropical region of Japan, this study
aims to characterize the epidemic patterns of influenza B infection and its association
32 with ambient temperature and relative humidity, in a parallel comparison with
influenza A.

34

Methods

36 From January 2007 until March 2014, two individual influenza surveillance
datasets were collected from external sources. The first dataset, included weekly rapid
38 antigen test (RAT) results from four representative general hospitals, located in the
capital city of Okinawa. A nation-wide surveillance of influenza, diagnosed by RAT
40 results and/or influenza-like illness symptoms, included the age distribution of
affected patients and was used as the second dataset. To analyze the association
42 between infection and local climate conditions, ambient temperature and relative
humidity during the study period were retrieved from the Japanese Meteorological
44 Agency website.

46 *Results*

Although influenza A maintained high number of infections from December
48 through March, epidemics of influenza B infection were observed annually from March

through July. The only observed exception was 2010, when the pandemic strain of 2009
50 dominated. During influenza B outbreaks, influenza patients aged 5 to 9 years old and
10 to 14 years old more frequently visited sentinel sites. Although both ambient
52 temperature and relative humidity are inversely associated with influenza A infection,
influenza B infection was found to be directly associated with high relative humidity.

54

Conclusion

56 Further studies are needed to elucidate the complex epidemiology of influenza B
and its relationship with influenza A. In the subtropical setting of Okinawa, epidemics
58 of influenza B infection occur from March to July following the influenza A epidemic,
and primarily affect school-age children. These findings help to define unknown
60 aspects of influenza B and can inform healthcare decisions for patients located outside
temperate regions.

62

64 **Key words**

influenza B, epidemics, seasonality, school-age, climate condition, temperature,
66 humidity

68 **Background**

70 Influenza A virus mutates frequently to escape the host immune system and
often causes epidemics. Historically, this had led to pandemics. Thus, influenza A
infection is regarded as important to both medical and social concerns [1, 2].
72 Alternatively, influenza B virus mutates less frequently than influenza A virus [3, 4].
Although some regional outbreaks are due to influenza B virus [5-8], the virus has
74 never caused a documented pandemic. Consequently, most epidemiological studies
have focused on influenza A infection rather than influenza B infection.

76 In temperate regions, it is well established that epidemics of influenza A often
occur during the winter [3]. However, in tropical and subtropical regions, influenza A
78 infections have been observed throughout the year [9]. In contrast, seasonal
information for influenza B is limited and epidemic patterns of influenza B can vary
80 among investigations [10, 11]. Again, most climate analysis studies have focused on
influenza A infection; data regarding influenza B infection is lacking considerably [10,
82 11].

In Japan, the universal healthcare system supports all citizens to visit outpatient
84 clinics, or the emergency departments of general hospitals, without referral. As a result,
patients with mild disease, including upper respiratory tract infection, often visit
86 general hospitals directly. In many cases, attending physicians suspecting an
influenza-like illness (ILI) will use a rapid antigen test (RAT), which can detect
88 influenza A and B separately [12]. In Okinawa, four representative general hospitals
aggregate and report the weekly results of the RATs. Using this routine surveillance
90 data, our investigative team previously reported the epidemic pattern of influenza A
viral infection and its relationship to climatic conditions [13, 14]. This retrospective

92 study aims to characterize the epidemic patterns of influenza B by combining the
aforementioned RAT reported results with the nation-wide influenza surveillance data
94 accumulated between 2007 and 2014. Our multicenter approach includes patients from
Okinawa, an important surveillance region in subtropical Japan. Influenza A in this
96 study is included for comparison.

98

Methods

100 *Dataset 1- local surveillance of influenza virus infection by rapid antigen test*

The clinical laboratories of four representative general hospitals, Naha City
102 Hospital (470 beds), Okinawa Red Cross Hospital (314 beds), Okinawa Prefectural
Nanbu Medical Center (434 beds), and Urasoe General Hospital (311 beds), in the
104 capital city of Okinawa, reported the results of the RATs for influenza virus weekly to
the Clinical Laboratory Center of the Medical Association. Data accessed from the
106 Clinical Laboratory Center of the Medical Association included only the total number
of tests administered and the number of positive influenza A, B, or A/B co-infected
108 results. Patient information and symptomatology were not available.

110 *Dataset 2- Japanese national sentinel surveillance data*

The Japanese national influenza surveillance is conducted in approximately 5,000
112 sentinel healthcare facilities throughout Japan; 55 facilities are within the Okinawa
Prefecture [15]. Data from these 55 sentinel healthcare facilities within Okinawa was
114 extracted from the Infectious Diseases Weekly Reports, published by the National
Institute of Infectious Diseases in Japan [16, 17]. This surveillance dataset includes the

116 age distribution of patients diagnosed with an influenza infection based on either a
positive RAT result and/or the presence of symptoms from ILI. Influenza-like illness is
118 defined with four criteria as follows; 1) acute onset of symptoms, 2) high fever, 3)
upper respiratory symptoms, and 4) general symptoms such as malaise, headache, and
120 myalgia. Patients with either a positive RAT result or who meet all four ILI criteria can
be added to the database.

122

Evaluation of age distribution of influenza A or B infection

124 Weekly disease patterns were monitored in dataset 1 retrospectively. A week in
which influenza A or B cases accounted for more than 90% of all positive influenza
126 cases was subsequently defined as an "epidemic week" for either influenza A or B,
respectively. Weeks with no predominant influenza type (i.e., A to B ratio was 1:1)
128 were not considered as "epidemic weeks" and were excluded from age distribution
analysis. Weeks determined as "epidemic weeks" in dataset 1 were matched to the
130 corresponding week in dataset 2. Patient age distribution from those corresponding
weeks was extracted from dataset 2 for the sentinel sites located within the Okinawa
132 Prefecture. A visual representation for this method is provided in Supplemental Table
1.

134

Geographic and climatic background

136 Okinawa Island is located in the East China Sea approximately 640 kilometers
south of the rest of Japan, and roughly 500 kilometers north of Taiwan. Possessing a
138 diverse native population, a large population of semi-permanent foreigners, and an
ample tourist trade, Okinawa has proven its worth as a surveillance site for the

140 monitoring of circulating respiratory viruses prior to epidemic outbreaks in mainland
Japan [18]. Average temperatures are 18 °C in winter and 28 °C in summer. The
142 island's subtropical climate supports a dense forest and a rainy season occurring in the
late spring. Daily climate data including ambient temperature and relative humidity
144 was retrieved from the Japanese Meteorological Agency website
(<http://www.data.jma.go.jp/jma/index.html>) [19]. Weekly climate variables were
146 calculated using the retrieved data.

148 *Statistical analysis*

The duration of infectious activity was assessed using the maximum proportion
150 of cases during consecutive weeks and the minimum number of weeks during which
there were at least 80% positive RAT results, a method previously described by Caini S,
152 et al [20]. Positive RAT cases and climate variables were evaluated by Spearman's
correlation coefficient test (one sided). The datasets used in this study can be found
154 within the additional files. Statistical analyses were performed using the SPSS software
(version 20.0, IBM Tokyo, Japan).

156

158 **Results**

From January 2007 to March 2014, 168,874 RATs were performed within the four
160 representative hospitals. The use of RATs diagnosed a total of 37,309 and 7,277
influenza A and influenza B infections, respectively. The incidence of influenza B
162 infection was lowest for 2010, the year following the influenza pandemic of 2009. The
annual number of influenza B positive cases ranged from 107 (0.9% of all RATs in 2010)

164 to 1,940 (9.5% of all RATs in 2011), as shown in Table 1. Co-infection with both A and B
was not common. Figure 1 shows the percentage of positive cases for influenza B was
166 less than influenza A. Epidemic analysis of influenza B revealed bimodal peaks
observed in March and May (data not shown). The middle 80% of influenza B
168 infections were seen from week 11 (middle March) to week 30 (end July), in contrast to
the middle 80% of non-pandemic strain influenza A cases occurring from week 51 (end
170 December) until week 13 (middle March) of the following year. Influenza A infection,
in seasons other than winter, was primarily attributed to the pandemic strain of 2009
172 (Figure 2).

Epidemic curves from the two datasets were aligned and analyzed to define at
174 risk age groups (Figure 3). Overall, patients aged 0 to 9 years old or 10 to 19 years old
more frequently visit the sentinel sites included in dataset 2 (lower) during periods of
176 influenza B outbreaks reported in dataset 1 (upper). An additional analysis of age
categories was conducted to validate these results. Age categories of the patients
178 affected by either influenza type were determined using the method depicted in
Supplemental Table 1. This method subsequently defined, 173 weeks with influenza A
180 cases >90% (148,244 assumed influenza A cases) and 78 weeks with influenza B cases
>90% (13,606 assumed influenza B cases). Age dynamics from weeks categorized as
182 influenza B weeks show 5 to 9 year-olds (28%) and 10 to 14 year-olds (25%) as the
predominant age groups seeking healthcare for confirmed or probable cases of
184 influenza. The same age patterns were not observed for influenza A weeks (Figure 4).

Finally, the impact of climate variables on the proportion of positive influenza A
186 or B results was evaluated on a weekly basis. As shown in Figures 5 and 6, a higher
proportion of influenza A positive cases were observed during periods of lower

188 ambient temperature and lower relative humidity. Alternatively, a high proportion of
influenza B positive cases were observed during times of high relative humidity. No
190 association between ambient temperature and influenza B could be determined.

192

Discussion

194 Okinawa's annual influenza B epidemics primarily occur between March and
July and display bimodal peaks in March and May. Although Kikuchi et al. reported a
196 2006 epidemic of influenza B from May to June in Sapporo, Japan [6], epidemics of
influenza B infection are rarely reported from mainland Japan and other temperate
198 regions. However, intermittent epidemics of influenza B have been reported from
Taiwan [21]. Also, a recently published article by the Global Influenza B Study Team
200 examined the cooperation and coordination of influenza A and B viruses. Together,
influenza A and B's combined effect successfully extended the influenza season for
202 countries located within tropical and subtropical regions [20]. Similarly, the
sub-tropical climate of Okinawa may enable the seasonal patterns of influenza
204 infection observed in the present study.

It is common knowledge that cold, dry weather can produce favorable conditions
206 for influenza A virus transmission [22-24]. It is also known that influenza A virulence
is considered greater than that of influenza B virus due to genetic shift and drift [2, 25,
208 26]. Following a winter with influenza A infection in decline, it is possible, influenza B
virus could more easily spread among those with weakened immunity. Additionally,
210 the dynamics among viruses themselves can influence patterns of epidemics. As we
have seen with the pandemic strain in 2009-2010, influenza A has the ability to

212 suppress outbreaks of other respiratory viruses, particularly influenza B [27]. Thus, the
differences in pathogenicity between influenza A and B could also explain the seasonal
214 patterns observed in Okinawa. Ultimately, the characteristics of influenza epidemics
for tropical and subtropical countries are complex and still poorly understood. In
216 reality, the interaction of several climatic and ecological drivers, including temperature,
humidity, altitude precipitation, population density and cultural mores or gathering
218 events could create the ideal setting for pervasive circulation.

In the present study, we were able to assess the association between the incidence
220 of influenza A or B infection and limited climatic conditions. Influenza A virus
remained significantly associated with cold and dry climate conditions [22-24].
222 However, the association between influenza B infection and climatic conditions was
less distinctive. Our analysis confirmed a high percentage of influenza A positive cases
224 were observed during periods of lower ambient temperature and lower relative
humidity. On the other hand, a high percentage of influenza B cases were associated
226 with high humidity. No link was observed between influenza B infection and
temperature (Figure 5, 6). In this study, we use relative humidity not specific humidity,
228 which may limit the accuracy of our results. Previous investigations from our team
have also used relative humidity [13, 14], and the standardization of the method was
230 important to compare this current study with previous data. Recent articles have
reported specific humidity is a better predictor of epidemics of influenza [28, 29].
232 Therefore, further analysis using specific humidity is needed to clarify the relationship
between influenza B and humidity in Okinawa. Since multiple factors are involved in
234 determining region-specific epidemic patterns of influenza infection [30], more
prospective epidemiological studies, including analyses of meteorological factors, are

236 needed to understand the circumstances found in Okinawa and other tropical and
subtropical regions.

238 During influenza B epidemics, our results showed the primary patient group
visiting healthcare facilities in Okinawa was school-age children (Figure 3, 4).

240 Alternatively, influenza A affects a much broader age range, suggesting that this
phenomenon is unique to influenza B infection. The pathogenicity of influenza A virus
242 is considerable and all age-groups are susceptible to influenza A infection [3, 16]. As a
result of this virulence, differences in prevalence among each age-group might become
244 less distinct. Influenza B virus cannot cause massive epidemics among all age-groups
due to its relatively weak virulence. Other reports also show that influenza B patients
246 were younger than influenza A patients [10, 11].

Healthcare seeking behavior may also account for the different patterns observed
248 among the age groups. It is well known that the school-age population can easily
spread influenza infections [31-34]. Working adults might be less likely to visit a clinic
250 with only mild symptoms due to influenza B infection. However, parents of school age
children may be more likely to seek immediate care for a sick child, regardless of
252 severity of symptoms. Additionally, acquired immunity within the host may account
for the observed differences among the age groups. Adults with repeated exposure to
254 influenza B may be less susceptible to the disease, since mutation rates for influenza B
are not as rapid as influenza A [35].

256 This study has some limitations. First, sample collection and laboratory analysis
were performed externally. The results of RATs performed in four representative
258 general hospitals in Okinawa is routinely accumulated and summarized on a weekly
basis. In addition, Japan has a nation-wide influenza surveillance system with weekly

260 reports available to all physicians. All data was received either through the local
prefectural influenza reporting system or through the Japanese national influenza
262 reporting system. Due to this external processing, patient details such as gender,
co-morbidities, and accompanying symptoms could neither be accessed nor analyzed.
264 Nevertheless, the Western Pacific Region Global Surveillance and Response System has
set precedent that surveillance data for ILI symptoms and datasets based on influenza
266 viral detection can be synchronized [25]. Our data replicates this method and
confirmed the epidemic curves of the two different datasets overlapped in Okinawa
268 (Figure 3).

A second limitation is the lack of standardization in RAT protocols and
270 manufacturers. Due to retrospective nature of this study and the diversity of hospitals
reporting data, there was no way to standardize which RAT test was implemented.
272 Okinawa serves as an important surveillance point to monitor the circulating strains of
influenza [13, 18]. Therefore, physicians in Okinawa are perpetually aware and use
274 RATs for patients with ILI, regardless of the season. As a result, usage of RATs for
patients with ILI is higher than average. Overall, the diagnostic accuracy of RATs sold
276 in Japan is high. At one point in 2013, 17 different RATs for influenza virus were
available in Okinawa. According to the included manufacturer's documents, the
278 sensitivity and specificity of RATs for influenza A virus, when compared with a gold
standard viral culture, ranged from 87.9 - 100% and 88.8 - 100%, respectively. Detection
280 of influenza B virus ranged from 80.4 - 100% and 90.7 - 100%, respectively. However,
RAT results should be expected to show significant heterogeneity due to differences in
282 patient age, virus type and brand variety, all of which can affect test results.

Furthermore, some studies describe lower sensitivity for detection of influenza B

284 infection than that of influenza A infection [12, 36-39]. This decrease in sensitivity may
cause even lower rates of detection for influenza B, due to increased false negative
286 results in some populations.

Lastly, this study did not investigate any patient factors with influence on
288 immunity, mainly, vaccination. In Japan, a quadrivalent vaccine against influenza
viruses was introduced in the 2015-16 season. However, the administration of
290 influenza vaccine is generally recommended before winter, and it is doubtful if the
efficacy of vaccine against influenza B infection lasts until spring. In the future,
292 discussions regarding the efficacy and the cost effectiveness of the single quadrivalent
vaccine compared to a bi-annual vaccine schedule should be considered if a decrease in
294 influenza infections is not achieved in Okinawa.

296

Conclusion

298 In Okinawa, influenza B epidemics primarily occur from March until July with
bimodal peaks in March and May and predominately affect school-age children. Our
300 data suggests high relative humidity may increase rates of influenza B infection. No
novel information was discovered regarding our comparator, influenza A, from this
302 study. Additional studies within the surveillance site of Okinawa, or other subtropical
regions are needed to confirm our results and expand our knowledge regarding the
304 epidemiology of influenza B.

306

308 **Declarations**

List of Abbreviations

310 RAT; rapid antigen test. ILI; influenza-like illness

312 *Ethics approval and consent to participate*

This study was approved by the Institutional Review of Board of the University of the
314 Ryukyus. This was a retrospective study and data were anonymously collected. There
was no additional disadvantage for the subjects.

316

Consent to publish

318 Not applicable

320 *Availability of data and materials*

The datasets used in this study can be found within the additional files.

322

Competing interests

324 Authors declare that they have no conflict of interests.

326 *Funding*

None

328

Authors' contributions

330 YI planned this study, collected and analyzed data, and prepared manuscript. TK
supervised this project and prepared manuscript with YI and GP. FH organized this

332 study, analyzed data. HM collected surveillance data. JF organized and supervised this
project.

334

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456

458 **Figure legends**

Figure 1: Epidemiology of influenza virus infection in Okinawa, Japan.

460 Gray and black bars indicate the percent of positive RATs for influenza A and B
infection among RATs performed, respectively, between 2007 and 2014 from four
462 representative hospitals.

464 Figure 2: Pooled number of positive cases of influenza infection by week.

Gray and hashed bars indicate the number of positive cases determined by rapid
466 antigen test (RAT) for influenza A and B infection, respectively. Cases are pooled for
each week from 2007 until 2014 using the RAT results from four representative
468 hospitals. Triangles indicate the number of influenza A infections determined by RAT
during the pandemic year of 2009 from four representative hospitals (from June 2009 to
470 March 2010).

472 Figure 3: Matched analysis of the two datasets.

Upper figure shows dataset 1 monitoring for the incidence of influenza A and B
474 infection from four representative hospitals in Okinawa. Lower figure shows the
distribution of each age group among influenza patients in dataset 2.

476

Figure 4: Age category distribution during epidemic weeks defined as influenza A or B
478 infection.

Epidemic weeks of influenza A or B were identified using the described method within
480 dataset 1. Information regarding age distribution for all identified weeks was extracted
from dataset 2. Assumed cases of influenza A and B totaled 148,244 and 13,606,

482 respectively. Only patient data from the 55 sentinel sites located within Okinawa was
used for age comparison.

484

Figure 5: Ambient temperature's effect on influenza infections in Okinawa, Japan

486 The relationship between ambient temperature and the percent of positive influenza A
or B infection for RAT results performed in four representative hospitals was analyzed
488 with Spearman rank correlation coefficient (one-sided). r ; correlation coefficient,
 p ; p value

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Figure 6: Relative humidity's effect on influenza infections in Okinawa, Japan

492 The relationship between relative humidity and the percent of positive influenza A or
B infection for RAT results performed in four representative hospitals was analyzed
494 with Spearman rank correlation coefficient (one-sided). r ; correlation coefficient,
 p ; p value

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Table 1: Result of rapid antigen tests performed in four general hospitals in Okinawa.

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Year	Number of tests performed	Influenza A positive	Influenza B positive	Influenza A/B positive
2007	19,229	5,143 (26.7%)	623 (4.4%)	6 (0.04%)
2008	13,089	1,878 (14.3%)	797 (7.1%)	4 (0.04%)
2009	41,962	12,741 (30.4%)	1,153 (3.9%)	18 (0.06%)
2010	13,825	2,508 (18.1%)	107 (0.9%)	2 (0.02%)
2011	24,468	4,128 (16.9%)	1,940 (9.5%)	7 (0.04%)
2012	27,148	5,284 (19.5%)	1,353 (6.2%)	4 (0.02%)
2013	18,494	2,475 (13.4%)	728 (4.5%)	0 (0.00%)
2014 (Jan. to Mar.)	10,659	3,152 (29.6%)	576 (7.7%)	1 (0.01%)
Total	168,874	37,309 (22.1%)	7,277 (4.3%)	42 (0.03%)

510

512 The annual number of rapid antigen tests (RAT) performed and reported positive
 results for influenza A, B, and A/B co-infected patients in four representative hospitals
 514 in Okinawa, Japan.

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522 Supplemental Table 1. Example weeks from dataset 1 and dataset 2 post-alignment.

Year	Week	Dataset 1 (RAT)			Dataset 2 (Age groups)										
		A (%)	B (%)	A/B (%)	0-4	5-9	10-14	15-19	20-29	30-39	40-49	50-59	60-69	70-79	80-
2007	9	377 (95.7)	17 (4.3)	0 (0)	388	309	304	156	254	232	103	86	29	30	13
2011	17	20 (7.7)	241 (92.3)	0 (0)	165	324	244	127	84	66	29	11	13	8	8
2013	18	14 (20.6)	54 (79.4)	0 (0)	37	54	44	18	27	28	18	12	2	6	4

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Sample weeks shown here are to serve as a visual representation of the method
 528 outlined to evaluate age distribution. Dataset 1 (left) and dataset 2 (right) were
 combined and aligned following the selection of "epidemic weeks". A week in which
 530 influenza A or B cases accounted for more than 90% of all positive influenza cases was
 defined as an epidemic week. In the year 2007, you see an example of a defined
 532 influenza A epidemic week, whereas the year 2011 is a representative influenza B
 epidemic week. The week from 2013 displays a typical week which was removed from
 534 our age distribution analysis because neither influenza A nor B was dominant (>90%).