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MAJOR ARTICLE

Population-based hospitalization burden of lineage specific influenza B children in Hong Kong, 2004-2014

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ABSTRACT

Background: Influenza B virus has been perceived to cause less disease burden and milder disease when compared to influenza A, but recent studies suggest influenza B does have a significant impact. We aimed to estimate the burden of influenza B virus infections on hospitalizations in Hong Kong, in the context of virus lineage changes over time.

Methods: The pediatric age-specific rates of influenza B hospitalization in Hong Kong for 2004-2014 were estimated based on admissions to two hospitals that together catered for 72.5% of all pediatric admissions on Hong Kong Island. Influenza B virus was detected by immunofluorescence and culture on nasopharyngeal aspirates. Lineage typing was performed by RT-PCR.

Results: A total of 5085 children were recruited on one designated day each week, year-round during the 11 years, and 221 (4.3%) tested positive for influenza B. Hospitalization rates were highest in children aged 2-<5 years with year to year variation. Victoria-lineage viruses appeared to be associated with a greater fraction of influenza B hospitalizations in children than of influenza B infections in the general community. Influenza B did not cause significant hospitalization in infants <1 year of age.

Conclusions: We report one of the first population-based age-specific and lineage-specific studies of pediatric hospitalization for influenza B. We found that changes in lineage were associated with higher hospitalization rates and we documented that Victoria lineage viruses were associated with greater pediatric hospitalization burden compared with Yamagata lineage viruses.

INTRODUCTION

Influenza leads to a significant burden of hospitalization in children annually. Influenza B was first identified in 1940 and two antigenically distinct virus lineages emerged in the mid-1980s, designated as the B/Yamagata and B/Victoria lineages [1]. Influenza B has been perceived to be associated with a lower disease burden and milder disease when compared to influenza A, but some recent studies have suggested that influenza B also causes significant mortality and morbidity [2,3]. Most studies on influenza B burden have not been able to estimate population-based incidence but are reports on frequencies of hospital admissions without defined population denominators. We previously published a study encompassing the influenza seasons of 2003-04 to 2005-06 that documented year to year variations in influenza B hospitalization [4]. In the current study, we report the age-specific hospitalization disease burden of influenza B in children in Hong Kong over an 11-year period.

METHODS

Study design

The Hong Kong Special Administrative Region (SAR) of China comprises of Hong Kong Island, Kowloon peninsular, the New Territories and some sparsely populated outlying islands. In 2006, there were 195,922 persons <18 years of age residing on Hong Kong Island [4]. Pamela Youde Nethersole Eastern Hospital and Queen Mary Hospital were the only two acute public hospitals on Hong Kong Island serving this population. These two hospitals, with a total of 153 pediatric beds, catered for 72.5% of all pediatric admissions from the population of Hong Kong Island in 2006 [4] (the remainder being admitted to private hospitals). While Hong Kong Island is not an entirely closed community, parents from other parts of Hong Kong SAR, namely Kowloon and the New Territories, rarely bring their children across the harbor for acute general pediatric problems since there are 10 public

hospitals with pediatric inpatient service serving those areas. Thus admissions can be related to the pediatric population resident on Hong Kong Island, allowing us to derive population based estimates of influenza associated hospitalization burden [4,5].

Acute respiratory infection was defined as fever ≥38°C (by history or documentation on admission) with any respiratory symptom including cough, runny nose, or sore throat. A systematic sample of all hospital admissions was derived by recruiting all patients aged <18 years of age with a Hong Kong Island home address admitted to either study hospital with acute respiratory infection during one designated day (24 consecutive hours) of the week. All recruited patients had a nasopharyngeal aspirate (NPA) specimen collected for virological testing.

The study protocol was approved by the joint Institutional Review Board of the University of Hong Kong and the Hospital Authority Hong Kong West Cluster, and the Hospital Authority Hong Kong East Cluster Research Ethics Committee which waived the need for written consent since the investigation was a routine diagnostic test carried out as part of routine care, and patient information was delinked from individual patient identification to maintain patient confidentiality.

Laboratory methods

NPA specimens from all recruited patients were tested for influenza B virus by direct antigen detection by direct immunofluorescence (IF) test, and by virus culture, at the Virology Laboratory at the University of Hong Kong and the Public Health Laboratory Services Branch, Centre for Health Protection, Department of Health, respectively. The direct immunofluorescence antigen test was carried out as previously described using IMAGEN^{TM}

respiratory screen and typing reagents (Oxoid Ely Ltd., UK) [6]. All the specimens found positive in the respiratory screen with a pooled IF reagent were further identified using antibody reagents to influenza B using the IMAGEN^{TM} typing kit.

Culture for respiratory viruses was done by inoculation 150 µl of the nasopharyngeal aspirate-virus transport medium suspension onto monolayers of continuous cell lines, including Martin Darby Canine Kidney (MDCK), African Green Monkey kidney (LLC-MK2), human epidermoid laryngngeal carcinoma (HEp-2C) and human embryonal rhabdomyosarcoma (RD), in culture tubes at the virology laboratory of the Department of Health as previously described [7]. This laboratory is the designated National Influenza Centre for Hong Kong within the World Health Organization (WHO) influenza laboratory network. MDCK was the cell line used for influenza virus isolation and inoculated cells were maintained in serum free medium with trypsin (2 µg/ml), and incubated at 33°C for 7 days. The cultures were examined daily for cytopathic effect and IF and hemagglutination inhibition tests were used for identification and antigenic characterization of influenza viruses respectively.

Influenza B lineages were differentiated by real-time PCR as described previously with modification [8]. Briefly, reaction conditions were established for the LightCycler 96 system in a total reaction mixture volume of 25 l containing 1X reaction mix (Invitrogen), 0.5 U SuperScriptIII Platinum RT Taq polymerase (Invitrogen), 900 nM forward primer (5-ACCCTACAR AMTTGGAACYTCAGG-3), 600 nM reverse primer (5-ACAGCCCAAGCCATTGTTG-3), 150 nM Yamagata probe MGB437 (5-FAM–AATCCGMTYTTACTGGTAG–MGB-3), 100 nM Victoria probe MGB470 (5-VIC–

ATCCGTTTCCATTGGTAA–MGB-3), and 5 l of RNA. Cycling conditions were 30 min at 50°C,then 2 min at 95°C, and followed by 50 cycles of 15 s at 95°C and 30 s at 55°C.

For comparison, we also obtained data on the community circulation of influenza B virus lineages in Hong Kong based on laboratory surveillance done by the virology laboratory of the Department of Health. In these surveillance data, approximately 95% of the positive results are detected from specimens from adult and pediatric patients hospitalized in public and private hospitals, the remainder are from out-patient clinics.

Statistical analysis

Hospitalization rates and 95% confidence intervals for each age group were estimated using Poisson regression models. The numerator in each incidence rate was the number of laboratory-confirmed influenza admissions in that age group, while the denominator was the estimated person-years at risk each year and was included in regression models as an offset term. The person-years at risk were estimated by the population of Hong Kong Island in that age group obtained from the Census and Statistics Department of the Hong Kong government based on regular population censuses, divided by 7 to allow for the study design of sampling one day per week, and further divided by 0.725 to arrive at the proportion of children served by the two study hospitals. Census data for infants under 6 months were lacking. Therefore, we used half the population under 1 year of age as the denominator, assuming a constant birth rate over the year. Statistical analyses were conducted using SAS version 9.02 (SAS Institute, Cary, NC) and R version 2.15.1 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

A total of 5085 children were included in the entire study spanning 11 years. Two hundred and twenty one children (4.3%) were tested positive for influenza B. Among all the hospitalized patients infected with influenza B, only 11 were <12 months of age. Of 436 infants <6 months, only four (0.9%) had influenza B virus infection when compared to 28 (6.4%) with influenza A virus infection and 98 (22.5%) with respiratory syncytial virus (RSV) infection. Likewise, of the 629 infants 6-12 months of age, seven (1.1%) had influenza B virus infection while 36 (5.7%) had influenza A virus infection and 108 (17.2%) had RSV infection. Of the 4020 children >12 months of age, 210 (5.2%) had influenza B infection compared to 440 (10.9%) with influenza A and 326 (8.1%) with RSV infection.

Of the 221 samples positive for influenza B, 175 were available for lineage analysis. Both lineages co-circulated in most years with the exception when a Yamagata lineage virus (in 2004 and 2007) or a Victoria lineage virus (in 2006) accounted for ≥95% of influenza B viruses identified (Table 1). There was almost no influenza B circulation in Hong Kong in 2009, the year when influenza A(H1N1pdm09) emerged. There was also very little influenza B circulation in 2013. In 2007, 2008, 2010, 2012 and 2014, influenza B circulation accounted for >3% of all respiratory samples from inpatients and outpatients tested by the government virology laboratory. There was no predictable seasonality with frequent overlap with that of influenza A. Influenza B caused hospitalization in almost all months in a few years (2007 and 2010) (Figure 1).

There was significant year to year fluctuation in disease burden in terms of pediatric hospitalizations due to influenza B in the 11 study years, largely correlating with influenza B circulation across the whole of Hong Kong (Figure 2A). Lineage-specific hospitalization

rates also fluctuated (Figure 2B). The proportion of children with chronic illness at high risk for influenza complications varied from year to year ranging from 11% to 38%. In general, hospitalization rates were consistently highest in children aged 2-<5 years and markedly higher in younger children below 2 years and older children 5-<10 years of age (Table 1). However, there was year to year variation. The rate of 38.7 per 10,000 in 2005 was significantly higher from that of 7.1 per 10,000 in 2004 (p=0.03) in the 2-<5 years group. There was also an apparent increase in hospitalizations in 2007 (65.6 per 10,000) when compared to 25.4 per 10,000 in 2006 and (p=0.06) in this age group when the predominant virus switched from a Victoria lineage virus to a Yamagata lineage virus. Influenza B did not appear to cause significant hospitalization in infants <1 year of age. Hospitalization in this age group was only documented in four of the 11 study years and all four years were dominated by circulation of the Yamagata lineage viruses after several years of Victoria lineage virus circulation.

The Victoria-lineage virus appeared to be associated with excess hospitalization in children when hospitalization is plotted against proportion of Victoria lineage viruses in circulation each year (Figure 3). In all of the confirmed influenza B hospitalizations included in this study, the mean age of hospitalized children was 6.0 years for B/Victoria vs 4.5 years for B/Yamagata (p=0.007) (Figure 4). With the exception of 2012, no infant <12 months of age was hospitalized for Victoria lineage virus infection.

DISCUSSION

In this study, we documented age-specific rates of hospitalizations due to influenza B lineages in children over a period of 11 years. Disease burden in terms of influenza B hospitalizations varied from year to year and has to be interpreted within the context of

overall virus activity, the influenza B lineages in circulation in each year, the emergence of antigenically different viruses, and influenza vaccination coverage. Athough we did not have complete vaccination data on all the patients in the present study, in a previously reported vaccine effectiveness study conducted between 2009 and 2014, we reported that influenza vaccination coverage is very low in children in Hong Kong with 8.8% in those hospitalized for a respiratory illness other than influenza B receiving influenza vaccine [9]. Meanwhile, two previous studies reported that 1.7% and 3.9% of pregnant women in Hong Kong were vaccinated during their pregnancy [10,11]. Therefore, the impact of influenza vaccination on hospitalization disease burden documented in this study is likely to be minimal.

It is commonly reported that influenza B mainly affects school aged children [12-14]. In this 11-year study, we also documented significant population based hospitalization rates in children 5-<10 years of age, but hospitalization rates were highest in children 2-<5 years (Table 1). In an earlier study of 2004-05 we also documented the highest hospitalization rates in the 2-<5 year age group [4]. This may reflect that influenza B virus infections in the younger age group were more likely to result in hospitalization, either due to more severe disease or a lower admission threshold in this younger age group. In a 20-year retrospective study of pediatric inpatients and outpatients from Finland, Peltola et al. found that outpatient consultation and hospitalization were highest in children <2 years [15]. A population-based study for children under 6 years in the US indicated that the age group with the highest influenza hospital admissions was infants <6 months while influenza A viruses were predominant during the study period [16].

Interestingly, unlike influenza A that resulted in the highest hospitalization in the youngest age group [5], we found that influenza B caused much lower hospitalization rates in infants

<12 months of age. Specifically, hospitalization of infants <6 months was only seen in three of the 11 years (Table 1). This was also documented in the Tecumseh Study which found no influenza B virus infections in 43 infants <1 year of age and only one patient in 135 patients 1-2 years of age (0.7%) [12]. Recently, a birth cohort study in Vietnam also showed that influenza B virus infection in infants <1y was rare [17]. Lineage characterization was not performed in these studies. The epidemiology of influenza B virus infections or hospitalization in this very young age is not well described in the literature because many influenza B studies focused on school age and older children. Protection from maternal antibodies may explain the very low incidence of influenza B hospitalization in these infants. Furthermore, the difference in hospitalization rates for influenza A and influenza B in very young infants may be explained by higher prevalence of protective maternal antibody against influenza B when compared to influenza A since influenza B viruses are believed to evolve more slowly than influenza A allowing for a higher background immunity against influenza B. In addition, there was hardly any hospitalization of infants <6 months of age due to Victoria lineage viruses even during a time of significant influenza B Victoria lineage circulation (Table 2). Unlike the rest of the world where the the Victoria lineages were not found between 1990s and early 2000, they have persisted in mainland China and Hong Kong since the 1980s [18,19]. Morevoer, Vijaykrishna et al. found that Victoria viruses were generally more transmissible than Yamagata viruses [20]. Thus it is likely that there would be a greater level of immunity to B/Victoria lineage viruses in women of child-bearing age in Hong Kong that may explain the low hospitalization rates in these young infants. Further studies to correlate maternal antibodies with infant infection of respective influenza B lineage would help to confirm this hypothesis.

Some previous studies have suggested that B/Victoria lineage viruses result in more infections or hospitalizations in the younger age groups (<15y) compared to B/Yamagata viruses in studies of all ages [19,21,22]. In this study of pediatric age groups, we provided age-specific rates and found that while the Victoria lineage viruses appears to cause higher rates of hospitalization, hospitalized children with B/Yamagata lineage viruses were in fact younger than those hospitalized with B/Victoria lineage viruses, and almost all hospitalizations in the <12 months group were attributed to B/Yamagata lineage viruses. Vijaykrishna et al. showed that Victoria lineage viruses have higher rates of antigenic drift, and expected the lower rates of antigenic drift of B/Yamagata lineage viruses to skew the age distribution of cases towards younger individuals after maternal antibody has waned [20]. Our study findings do support their hypothesis. A recent study from Bangkok did not compare hospitalization rates but concluded that the B/Victoria lineage viruses were associated with a longer duration of hospitalization, and a higher number of fatal cases and pneumonia [23]. However the study included all age groups with a trend towards a higher proportion of patients ≥65y in the B/Victoria lineage group.

An example of the impact of a change in lineage predominance was observed in 2007. In that year, Hong Kong had substantial influenza B activity (Figure 1) and we documented significant pediatric hospitalization in all months except January that year [25]. Yamagata lineage virus dominated with 95% of influenza B in circulation in Hong Kong following 2006 which was a year of Victoria lineage dominance (97%). The abrupt switch of lineage predominance may explain the high virus circulation and disease burden. The impact of emergence of a different clade could also be seen: in 2012, the Yamagata lineage viruses only accounted for 58% of influenza B in Hong Kong but there was an increase in hospitalization due to Yamagata lineage viruses including in infants 6-12 months of age that was not seen in

the previous two years (2010 and 2011) with similar ratio of Victoria to Yamagata lineage virus circulation (Table 2 and Figure 2). Although we did not perform antigenic analysis on the strains from our individual patients, WHO reported the emergence of clade 2 Yamagata lineage viruses that were antigenically different from the previously circulating clade 3 (B/Wisconsin/1/2010 Yam-like) viruses [26]. Again, in 2014, Yamagata lineage viruses accounted for 86% of influenza B viruses in Hong Kong and resulted in moderately high hospitalization rates in children. This might be due to the circulation of clade 3 viruses that were antigenically distinguishable from the vaccine strain B/Massachusetts/2/2012 which was a clade 2 virus [27]. Clade analysis on 30 Yamagata lineage viruses in that year showed that 27 indeed belonged to clade 3 (Lo et al. unpublished data).

There are a number of limitations to our study. Our study is based on children hospitlised with influenza B and we have no information on influenza B circulation in children in the general community. We included children who met our case definition of fever (or history of fever) plus at least one respiratory symptom and therefore may have excluded a small number of influenza B hospitalizations with atypical presentation. Furthermore, we do not have antigenic characterization of the individual strains from patients. However, viral circulation and antigenic analysis derived from the overall surveillance data in Hong Kong from the Department of Health provides some indication of viruses, lineages and antigenic variants circulating in the Hong Kong community overall.

In conclusion, we report one of the first population-based studies of pediatric hospitalization for influenza B by lineage. We found that hospitalization rates varied from year to year, largely corresponding to overall virus circulation within the community. We found that higher hospitalization rates correlated with changes in lineage. We documented that Victoria

lineage viruses were associated with greater excess hospitalization than might have been expected based on the proportion of viruses in circulation within the community (Figure 3). This study highlights the importance of interpreting influenza B disease burden in the context of antigenic changes and background viral activity.

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POTENTIAL CONFLICTS OF INTEREST:

BJC has received research funding from MedImmune Inc and Sanofi Pasteur and has consulted for Crucell NV. The authors report no other potential conflicts of interest.

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FIGURE LEGENDS

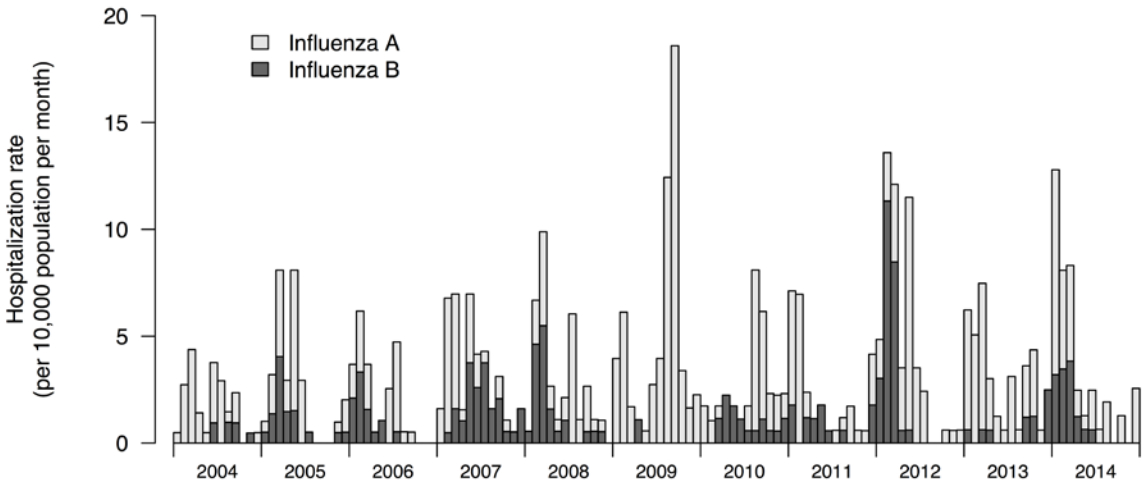

Figure 1. Rates of hospitalization associated with influenza B in children <18 years of age by calendar month from 2004-2014. Hospitalization rates for influenza A over the same period are also presented for comparison.

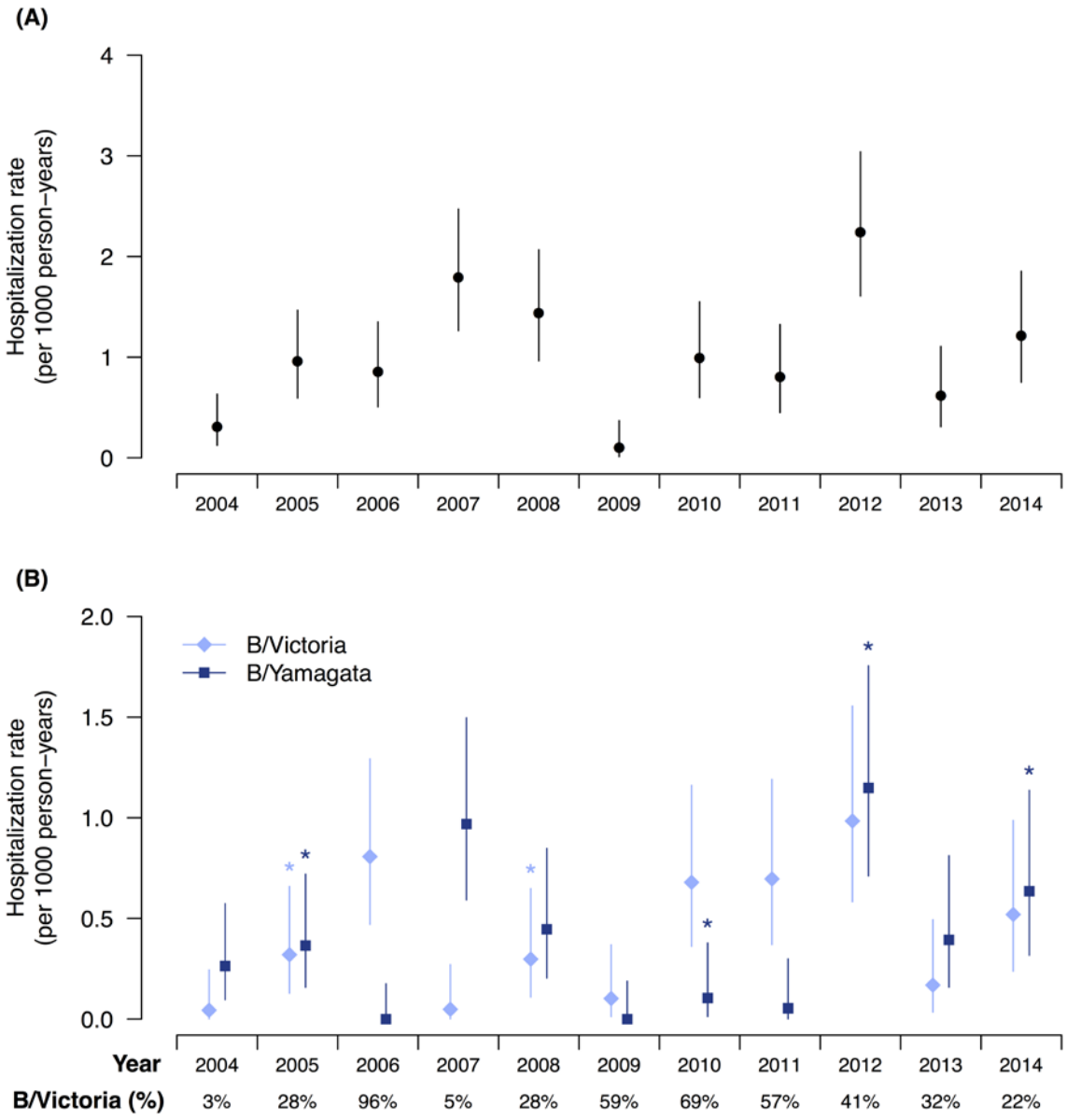

Figure 2. Annual hospitalization rates of paediatric patients infected with influenza B viruses overall (panel A), and identified as Victoria or Yamagata lineage (panel B) in Hong Kong from 2004 through 2014. An asterisk above particular estimates indicates the year when there was an antigenic change in the corresponding lineage. The bottom row reports the annual proportion of laboratory detections of influenza B cases belonging to Victoria lineage among all influenza B detections with lineage typing done. The proportions of laboratory detections of influenza B/Yamagata lineage virus among all influenza B detections can be calculated as one minus the proportion of B/Victoria detections, and are therefore not shown.

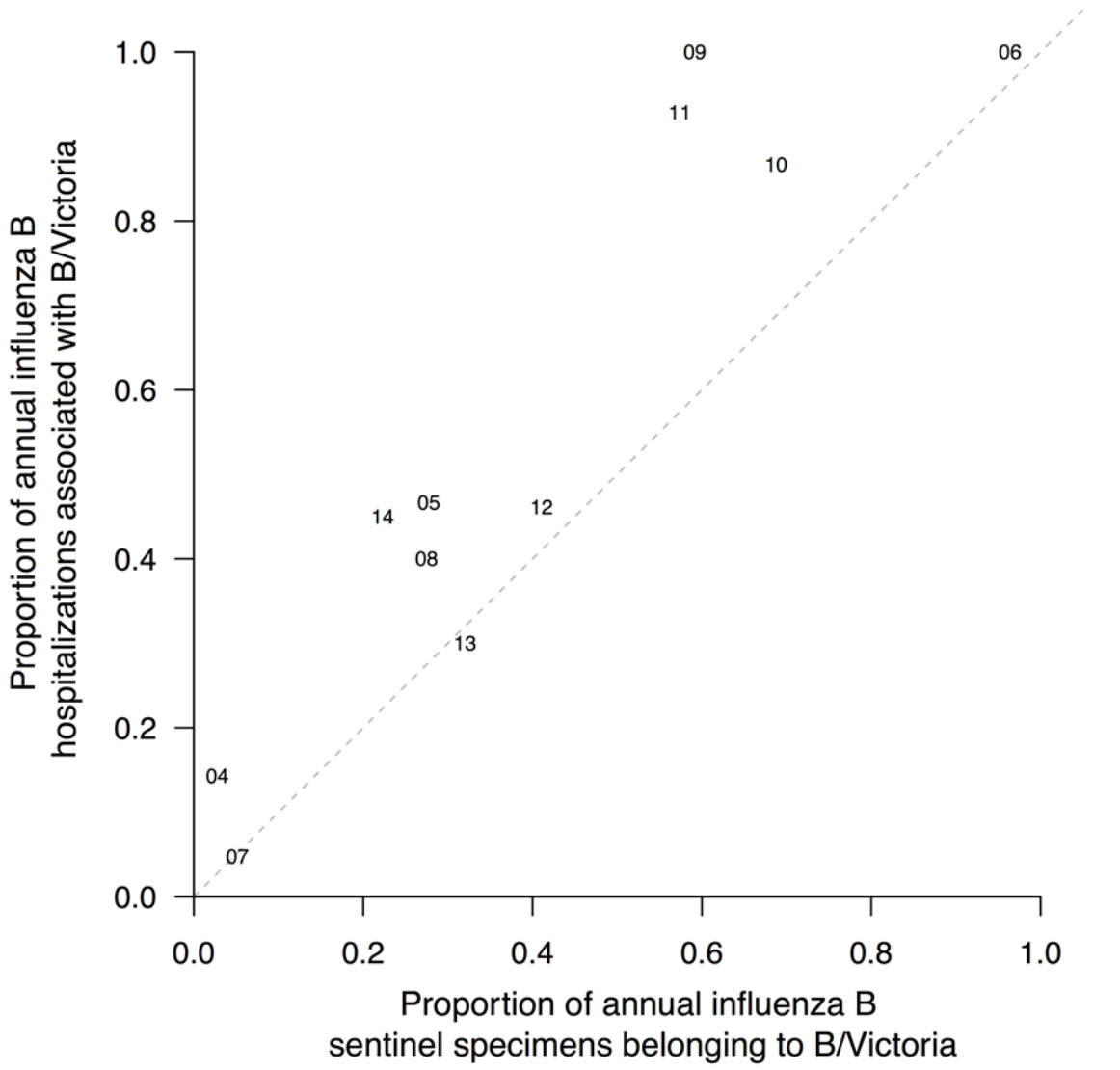

Figure 3. Association between the proportion of influenza B hospitalizations in children associated with B/Victoria viruses (y-axis) and the proportion of community detections of influenza B associated with B/Victoria viruses (x-axis) each year. Note that the proportion of B/Yamagata can be derived as one minus the proportion with B/Victoria. The two digits indicate the corresponding year in the 21st century, e.g. 09 corresponds to the calendar year of 2009. Points above the diagonal line indicate years in which the B/Victoria viruses were identified more frequently in hospitalized children with influenza B than among influenza B infections in the community. Points below the diagonal line indicate years in which the

B/Yamagata viruses were identified more frequently in hospitalized children with influenza B than among influenza B infections in the community.

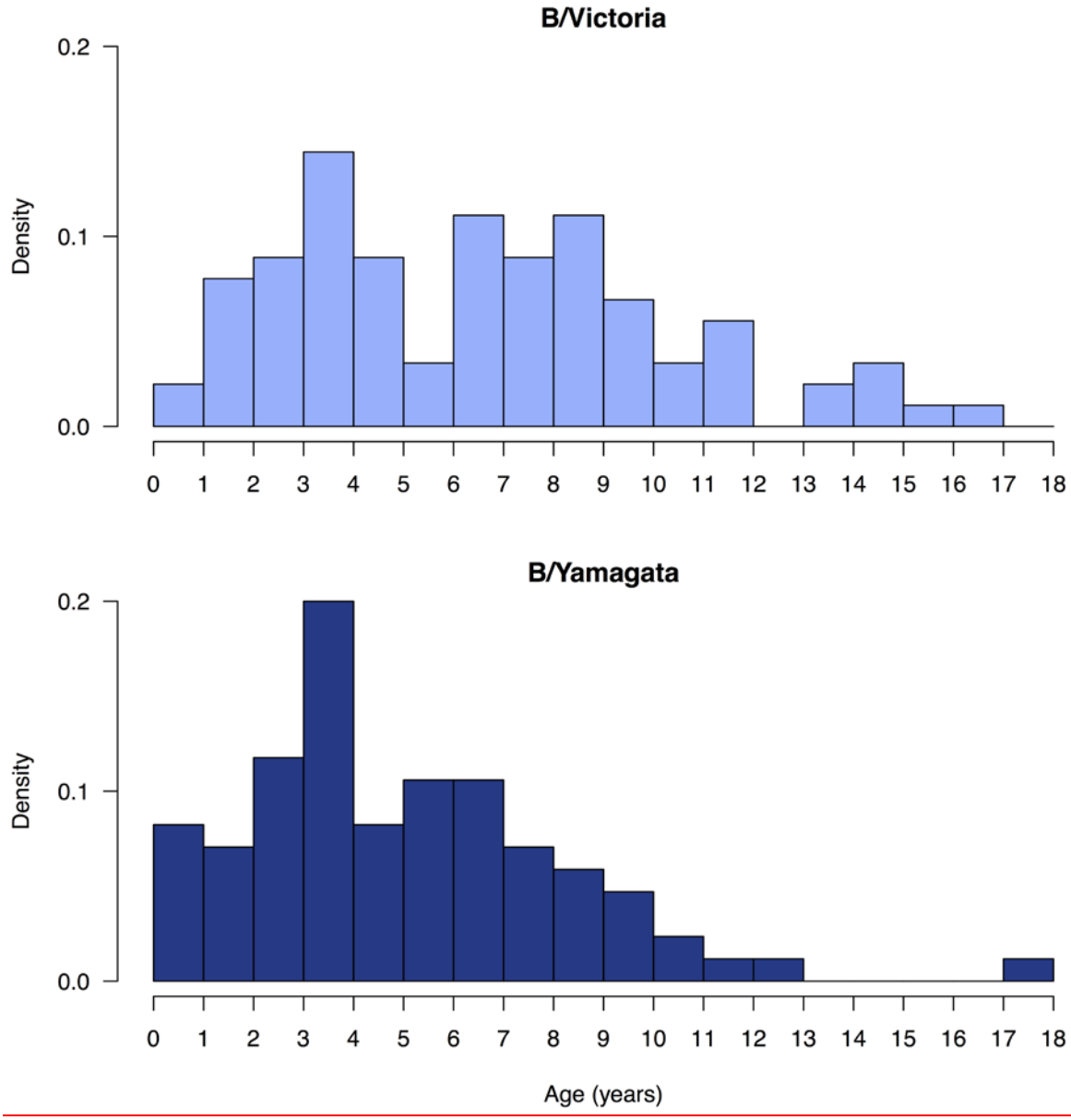

Figure 4. Age distribution of pediatric hospitalizations associated with B/Victoria and B/Yamagata lineage viruses.

Table 1. Age-specific rates of hospitalizations (95% confidence interval) associated with confirmed influenza B Yamagata or Victoria lineage per 10,000 residents, 2004-2011

Year	Predominant Lineage in Hong Kong (%)	<6m		6-12m		1-<2y		2-<5y		5-<10y		10-<15y		15-<18y	
		B / Yamagata	B / Victoria	B / Yamagata	B / Victoria	B / Yamagata	B / Victoria	B / Yamagata	B / Victoria	B / Yamagata	B / Victoria	B / Yamagata	B / Victoria	B / Yamagata	B / Victoria
2004	97% (Yam)-like	0	0	0	0	0	0	7.1	0	6.5	1.6	0	0	0	0
		(0, 86.7)	(0, 86.7)	(0, 86.7)	(0, 86.7)	(0, 44.4)	(0, 44.4)	(0.9, 25.7)	(0, 13.1)	(1.8, 16.6)	(0, 9.0)	(0, 5.2)	(0, 5.2)	(0, 8.8)	(0, 8.8)
2005	72% (Yam)-like	0	0	0	0	12.8	12.8	19.4	7.7	3.4	0	0	4.3	0	2.4
		(0, 91.1)	(0, 91.1)	(0, 91.1)	(0, 91.1)	(0.3, 71.4)	(0.3, 71.4)	(6.3, 45.2)	(0.9, 28.0)	(0.4, 12.4)	(0, 6.3)	(0, 5.3)	(0.9, 12.6)	(0, 8.9)	(0.1, 13.4)
2006	96% (Vic)-like	0	0	0	0	0	0	0	25.4	0	14.5	0	2.9	0	2.4
		(0, 95.7)	(0, 95.7)	(0, 95.7)	(0, 95.7)	(0, 50.3)	(0, 50.3)	(0, 15.6)	(9.3, 55.3)	(0, 6.7)	(6.3, 28.7)	(0, 5.4)	(0.4, 10.6)	(0, 9.0)	(0.1, 13.6)
2007	95% (Yam)-like	24.6	0	49.1	0	26.1	13.1	32.8	0	11.5	0	1.5	0	0	0
		(0.6, 136.8)	(0, 90.6)	(5.9, 177.4)	(0, 90.6)	(3.2, 94.4)	(0.3, 72.8)	(14.2, 64.6)	(0, 15.1)	(4.2, 25.0)	(0, 7.1)	(0, 8.5)	(0, 5.6)	(0, 9.1)	(0, 9.1)
2008	72% (Yam)-like	0	0	23.4	0	12.6	0	12.0	8.0	6.1	6.1	0	1.6	2.5	0
		(0, 86.2)	(0, 86.2)	(0.6, 130.2)	(0, 86.2)	(0.3, 70.0)	(0, 46.4)	(2.5, 34.9)	(1.0, 28.8)	(1.3, 17.7)	(1.3, 17.7)	(0, 5.9)	(0, 8.9)	(0.1, 14.1)	(0, 9.3)
2009	59% (Vic)-like	0	0	0	0	0	12.2	0	0	0	2.2	0	0	0	0
		(0, 82.5)	(0, 82.5)	(0, 82.5)	(0, 82.5)	(0, 44.8)	(0.3, 67.7)	(0, 14.4)	(0, 14.4)	(0, 8.0)	(0.1, 12.0)	(0, 6.2)	(0, 6.2)	(0, 9.5)	(0, 9.5)
2010	69% (Vic)-like	0	0	0	0	0	11.7	3.8	7.6	2.3	16.1	0	5.3	0	0
		(0, 78.8)	(0, 78.8)	(0, 78.8)	(0, 78.8)	(0, 43.2)	(0.3, 65.2)	(0.1, 21.1)	(0.9, 27.3)	(0.1, 12.8)	(6.5, 33.1)	(0, 6.6)	(1.1, 15.6)	(0, 9.7)	(0, 9.7)
2011	57% (Vic)-like	0	0	0	0	0	0	0	22.1	2.5	14.7	0	1.9	0	0
		(0, 75.4)	(0, 75.4)	(0, 75.4)	(0, 75.4)	(0, 41.7)	(0, 41.7)	(0, 13.6)	(8.1, 48.1)	(0.1, 13.7)	(5.4, 32.1)	(0, 6.9)	(0, 10.5)	(0, 9.9)	(0, 9.9)
2012	59% (Yam)-like	0	19.5	39.0	19.5	10.9	21.7	32.1	32.1	21.0	10.5	2.0	2.0	0	0
		(0, 72.0)	(0.5, 108.7)	(4.7, 140.9)	(0.5, 108.7)	(0.3, 60.5)	(2.6, 78.5)	(14.7, 61.0)	(14.7, 61.0)	(9.1, 41.4)	(2.9, 26.9)	(0.1, 11.0)	(0.1, 11.0)	(0, 10.0)	(0, 10.0)
2013	68% (Yam)-like	18.8	0	0	0	0	0	10.5	0	5.7	5.7	2.1	2.1	0	0
		(0.5, 104.6)	(0, 69.3)	(0, 69.3)	(0, 69.3)	(0, 38.8)	(0, 38.8)	(2.2, 30.6)	(0, 12.9)	(0.7, 20.6)	(0.7, 20.6)	(0.1, 11.8)	(0.1, 11.8)	(0, 10.3)	(0, 10.3)
2014	78% (Yam)-like	0	0	0	0	10.2	10.2	10.2	6.8	18.6	15.5	2.3	2.3	0	0
		(0, 66.6)	(0, 66.6)	(0, 66.6)	(0, 66.6)	(0.3, 56.7)	(0.3, 56.7)	(2.1, 29.8)	(0.8, 24.6)	(6.8, 40.4)	(5.0, 36.1)	(0.1, 12.6)	(0.1, 12.6)	(0, 10.5)	(0, 10.5)