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Citation	PLoS One, 2015, v. 10 n. 4, p. e0120983
Issued Date	2015
URL	http://hdl.handle.net/10722/218506
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RESEARCH ARTICLE

Surveillance for Seasonal Influenza Virus Prevalence in Hospitalized Children with Lower Respiratory Tract Infection in Guangzhou, China during the Post-Pandemic Era

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Citation: Guan WD, Gong XY, Mok CKP, Chen TT, Wu SG, Pan SH, et al. (2015) Surveillance for Seasonal Influenza Virus Prevalence in Hospitalized Children with Lower Respiratory Tract Infection in Guangzhou, China during the Post-Pandemic Era. PLoS ONE 10(4): e0120983. doi:10.1371/journal.pone.0120983

Academic Editor: Zhiping Ye, US Food and Drug Administration, UNITED STATES

Received: September 1, 2014

Accepted: February 9, 2015

Published: April 13, 2015

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Data Availability Statement: All relevant data are within the paper and its Supporting Information files. The data points used to determine any summary statistics presented in the figures and tables have been included.

Funding: This study was financially supported by Municipal Science and Technology Bureau Foundation of Guangzhou (Grant no. Grant no. 2014Y2-00031), Emergency Response Project of Ministry of Science and Technology of China (Grant no. KJYJ-2013-01-05), National Science and

Abstract

Background

Influenza A(H1N1)pdm09, A(H3N2) and B viruses have co-circulated in the human population since the swine-origin human H1N1 pandemic in 2009. While infections of these subtypes generally cause mild illnesses, lower respiratory tract infection (LRTI) occurs in a portion of children and required hospitalization. The aim of our study was to estimate the prevalence of these three subtypes and compare the clinical manifestations in hospitalized children with LRTI in Guangzhou, China during the post-pandemic period.

Methods

Children hospitalized with LRTI from January 2010 to December 2012 were tested for influenza A/B virus infection from their throat swab specimens using real-time PCR and the clinical features of the positive cases were analyzed.

Results

Of 3637 hospitalized children, 216 (5.9%) were identified as influenza A or B positive. Infection of influenza virus peaked around March in Guangzhou each year from 2010 to 2012, and there were distinct epidemics of each subtype. Influenza A(H3N2) infection was more frequently detected than A(H1N1)pdm09 and B, overall. The mean age of children with influenza A virus (H1N1/H3N2) infection was younger than those with influenza B (34.4 months/

Technology Major Project of the Ministry of Science and Technology of China (Grant no. 2014ZX10004006). CKPM and BC were supported by funding by grant AoE/M-12/06 from the University Grants Committee, Hong Kong.

Competing Interests: The authors declare that co-author Benjamin Cowling is a PLOS ONE Editorial Board member. This does not alter the authors' adherence to PLOS ONE Editorial policies and criteria.

32.5 months versus 45 months old; $p < 0.005$). Co-infections of influenza A/ B with mycoplasma pneumoniae were found in 44/216 (20.3%) children.

Conclusions

This study contributes the understanding to the prevalence of seasonal influenza viruses in hospitalized children with LRTI in Guangzhou, China during the post pandemic period. High rate of mycoplasma pneumoniae co-infection with influenza viruses might contribute to severe disease in the hospitalized children.

Introduction

In March and April of 2009, cases of human infection with the swine origin human H1N1 influenza A virus were first detected in North America [1,2]. During the early outbreak, patients with confirmed influenza A(H1N1)pdm09 tended to present with relatively severe clinical symptoms such as respiratory failure and multiple organ damage [2–4]. However, a majority of cases were subsequently found to show a mild course of disease similar to the seasonal influenza virus infection [5]. In August 2010, the World Health Organization declared the start of the post-pandemic phase [6]. Infection with the influenza A(H1N1)pdm09 virus was first reported in China on May 11, 2009 and increased community transmission of this subtype was observed subsequently with a peak in activity in November 2009 [4].

It has been known that influenza A(H1N1)pdm09, A(H3N2) and B viruses have continued to circulate in populations after the pandemic period. A number of reports have documented the burden of influenza in the post-pandemic period from different countries [7–10]. However, there is very limited data on the contribution of influenza virus to the burden of hospitalization in children in China. Report showed that approximately 70% of hospitalized patients with influenza infection in severe acute respiratory infection (SARI) cases were children under 5 years old [8]. Children with influenza infection usually present with upper respiratory tract infection symptoms. However, some of them developed lower respiratory tract infection (LRTI) such as bronchitis or pneumonia, resulting in the need for hospitalization. During the pandemic period, we have established a surveillance system to monitor the burden of influenza in Guangzhou, which is the largest metropolitan city in Guangdong province. A three-year surveillance study from January 2010 to December 2012 was carried out in the city of Guangzhou to estimate the prevalence of influenza virus infection in the hospitalized children with LRTI in Guangzhou during the post pandemic period.

Materials and Methods

Subjects

A retrospective study was conducted in hospitalized children with LRTI at the First Affiliated Hospital of Guangzhou Medical University, which is a large tertiary referral hospital in Guangzhou. The inclusion criteria for the study were clinical diagnosis of LRTI defined as the presence of at least one respiratory symptom (cough, sputum production, dyspnea, tachypnea, pleuritic pain) along with at least one finding during auscultation (rales, crepitation), or one sign of infection (core body temperature $> 38.0^{\circ}\text{C}$, shivering, leukocyte count $> 10 \times 10^9/\text{L}$ or $< 4 \times 10^9/\text{L}$ cells) independent of antibiotic pretreatment.

Throat swab samples from the patients were tested for influenza A H1N1pdm09, seasonal H3N2 and influenza B virus infection using real-time RT-PCR as described previously [11]. The clinical features and other factors among the three infection groups were compared. This study was approved by the ethics committee of the First Affiliated Hospital of Guangzhou Medical University which was waived the need for written consent since virologic testing was a routine diagnostic procedure and patient information saved at the study database was delinked from individual patient identifiers. The infection of mycoplasma pneumoniae was determined by an indirect immunofluorescent assay kit (PNEUMOSLIDE IgM, Vircell) for the simultaneous diagnosis in human serum of IgM antibodies. The presence of bacteria from throat swab, induced sputum or bronchoalveolar fluid were identified by VITEK 2 Compact system (BioMérieux, France).

Statistical Analysis

GraphPad Prism 5 was employed for statistical analysis. Quantitative data are presented as the mean±standard deviation (SD) or median values with range. Normally distributed data were compared by analysis of variance(ANOVA); Otherwise, the non-parametric Kruskal-Wallis test was used. The categorical variables are reported as frequencies and percentages following comparison with Fisher's exact or a chi-square test. All hypothesis testing was two-sided; Levels of significance were set at a p value <0.05.

Results

Throat samples from 3637 children with LRTI were collected in Guangzhou from January 2010 to December 2012 and 216 samples were identified as influenza A/B positive (5.94%). Among the positive cases, 26 (12.04%) were influenza A H1N1pdm09, 131 (60.65%) were H3N2 and 59 (27.31%) were influenza B (Table 1). Generally, the peak of the detection rates occurred in March each year. After the pandemic period, the detections of influenza A(H1N1) pdm09 reappeared in February and March 2011. Influenza A(H3N2) virus predominated in 2010 and 2012. Influenza B virus was found to co-circulated with H3N2 but fewer cases were identified at the same period of time (Fig 1). The mean age of infection with influenza A H1N1pdm09, H3N2 and influenza B virus were 34.38 months, 32.47 months, and 45.04 months respectively (Table 1). Similar attack rate from all age groups was observed in those children infected with H1N1pdm09 and H3N2. Lower detection rates of influenza B/Yamagata were found in all age groups (less than 10%). However, over 40% of influenza B/Victoria cases were observed in children older than 48 months (Fig 2). We did not find any significant difference in the age distribution of B/Victoria versus B/Yamagata cases ($p = 0.50$; chi-squared test).

A higher proportion of the influenza positive cases were identified as pneumonia compared to acute bronchitis in admission diagnoses (H1N1pdm09: 76.9% vs 23.1%; H3N2: 71.0% vs 29.0%; B: 64.4% vs 35.6%). However, there was no significant difference among three groups ($p = 0.47$) (Table 1). We found that around 37–40% of the patients among the three groups presented gastrointestinal symptoms (H1N1pdm09: 38.5%; H3N2: 40.5%; B: 37.3%) (Table 1). Interestingly, a large proportion of influenza A/B infected hospitalized children were identified with mycoplasma pneumoniae (MP) co-infection. The co-infection rate is higher in the group of influenza A H1N1pdm09 (38.46%) infection compared to the groups of seasonal H3N2 (13.74%), or influenza B (27.12%) ($p < 0.05$) (Table 1). On the other hand, cases of co-infection with bacteria were rare in our study. The duration of hospitalization in influenza A (H1N1) pdm09, seasonal H3N2 and B group were 8.69 ± 5.55 days, 10.00 ± 7.25 days and 9.05 ± 3.51 days respectively ($p = 0.46$). All cases were discharged from our hospital and no patients died. We

Table 1. Clinical presentation and laboratory findings of the children with influenza virus infection.

Clinical Variables	A/H1N1 (pdm09) (n = 26)	A/H3N2 (n = 131)	B (n = 59)	P ¹	Clinical Variables	A/H1N1 (pdm09) (n = 26)	A/H3N2 (n = 131)	B (n = 59)	P ¹
Males	16	94	38	0.4304	Loss of appetite	7(26.9)	34(26.0)	16(27.1)	0.9838
Mean age±SD, m	34.4±34.1	32.5±34.6	45.0 ±32.5	0.0046	Stomachache	1(3.9)	3(2.3)	2(3.4)	ND
Febrile seizures	2(7.7)	5(3.8)	3(5.1)	0.6784	Diarrhea	1(3.9)	5(3.9)	2(3.4)	ND
Shivering	2(7.7)	11(8.4)	9(15.3)	0.3179	gastrointestinal symptoms	10(38.5)	53(40.5)	22(37.3)	0.9134
Fever²⁾	25(96.2)	116(88.5)	53(89.8)	0.0522	Crackles	15(57.7)	59(45.0)	21(35.6)	0.1550
Max Temp (°C)	39.13±1.04	39.20±0.74	39.22 ±0.96	ND	three-concave sign	1(3.9)	2(1.5)	2(3.4)	ND
Headache	2(7.7)	2(1.5)	2(3.4)	0.2053	Lymphadenopathy	4(15.4)	39(29.8)	21(35.6)	0.1705
Myalgia	0	0	5(8.5)	ND	Antiadoncus	14(53.9)	60(45.8)	36(61.0)	0.1445
Acratia	0	0	1(1.7)	ND	Throat herpes	1(3.9)	2(1.5)	2(3.4)	ND
Rhinocleisis	14(53.9)	46(35.1)	20(33.9)	0.1647	Co-infection of bacteria	0	6(4.6)	2(3.4%)	ND
Runny nose	14(53.9)	71(54.2)	27(45.8)	0.5470	Co-infection of Mycoplasma Pneumoniae	10(38.5)	18(13.7)	16(27.1)	0.0054
Sneezing	0	10(7.6)	5(8.5)	ND	Acute bronchitis	6(23.1)	38(29.0)	21(35.6)	0.4653
Trachyphonia	0	2(1.5)	1(1.7)	ND	Pneumonia	20(76.9)	93(71.0)	38(64.4)	0.4653
Cough	26(100)	129(98.5)	55(93.2)	ND	Duration of hospitalization	8.7±5.6	10.0±7.3	9.1±3.5	0.4645
Sputum production	5(19.2)	35(26.7)	19(32.2)	0.4657	Complication	4(15.4)	34(26.0)	13(22.0)	0.8221
Wheezing	6(23.1)	37(28.2)	8(13.6)	0.0877	Acute benign myositis	0	0	2(3.4)	ND
Tachypnea	2(7.7)	15(11.5)	4(6.8)	0.5797	Impaired liver function	1(3.9)	1(0.8)	0	ND
Vomiting	4(15.4)	21(16.0)	12(20.3)	0.7425	Cost median (RMB)	3765	3821	4254	0.4097

Data are shown as numbers (%) unless otherwise specified.

¹⁾ Comparisons were made among A(H1N1)pdm09, seasonal H3N2, and influenza B by using ANOVA for quantitative characteristics and Fisher's exact or chi-square test for categorical variables, respectively.

²⁾ Denotes the highest body temperature of feverish patients before and on admission to hospital.

ND: Not determined

doi:10.1371/journal.pone.0120983.t001

found that the cost of treatment of the children during hospitalization was similar among the three influenza subtypes (3765, 3821, 4254 respectively; $p = 0.41$).

Chronic respiratory disease appeared to be a risk factor for influenza among the children with LRTI (Table 2). However, no statistically significant differences were observed among the three infection groups with underlying conditions. A high proportion of children with the infection of influenza A(H1N1)pdm09, A(H3N2) and B were living in a secondhand smoking environment (50%, 50%, 46.78% respectively; $p = 0.99$). The proportion of caesarean was relatively high in each group of our study (46.15%, 44.27% and 44.07% respectively; $p = 0.98$)

Discussion

We conducted a retrospective surveillance study of influenza A/B infection in hospitalized children with LRTI in Guangzhou city during the post-pandemic period. This study was benefited from the establishment of a sentinel surveillance system for suspected SARS or avian influenza infection cases implemented since 2008. Data from our study showed that three virus subtypes are co-circulating in the community and influenza A (H3N2) was detected more frequently compared to H1N1pdm09 and influenza B among the hospitalized children with LRTI.

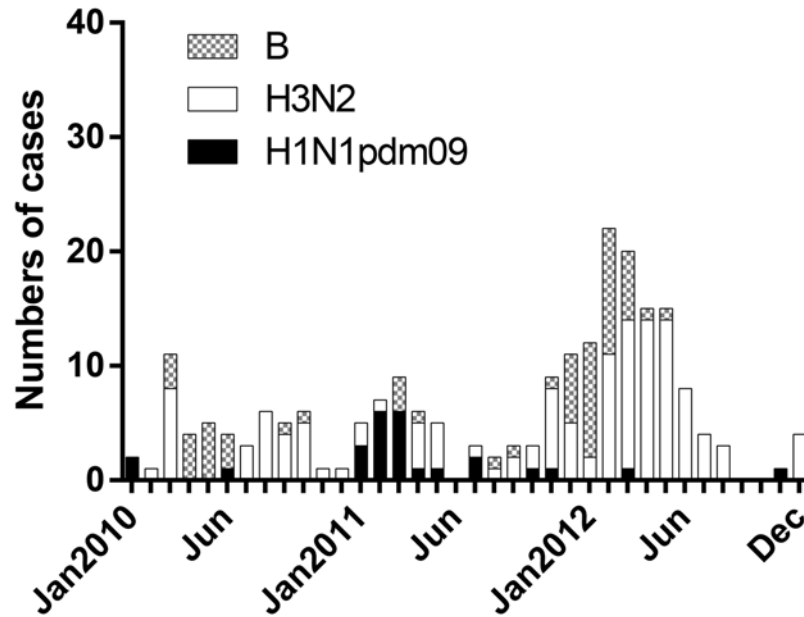


Fig 1. Number of influenza positive by subtype and by month of illness onset among the hospitalized children with lower respiratory tract infection (N = 3637), Guangzhou, China, January, 2010 to December, 2012.

doi:10.1371/journal.pone.0120983.g001

The prevalence of the influenza subtypes in hospitalized children with LRTI from this three-year study is consistent with previous findings from the study of outpatients with ILI in the GuangDong province [12]. In early 2010, infection cases of H1N1pdm09 declined dramatically while H3N2 and influenza B were predominant in the population until the end of 2010.

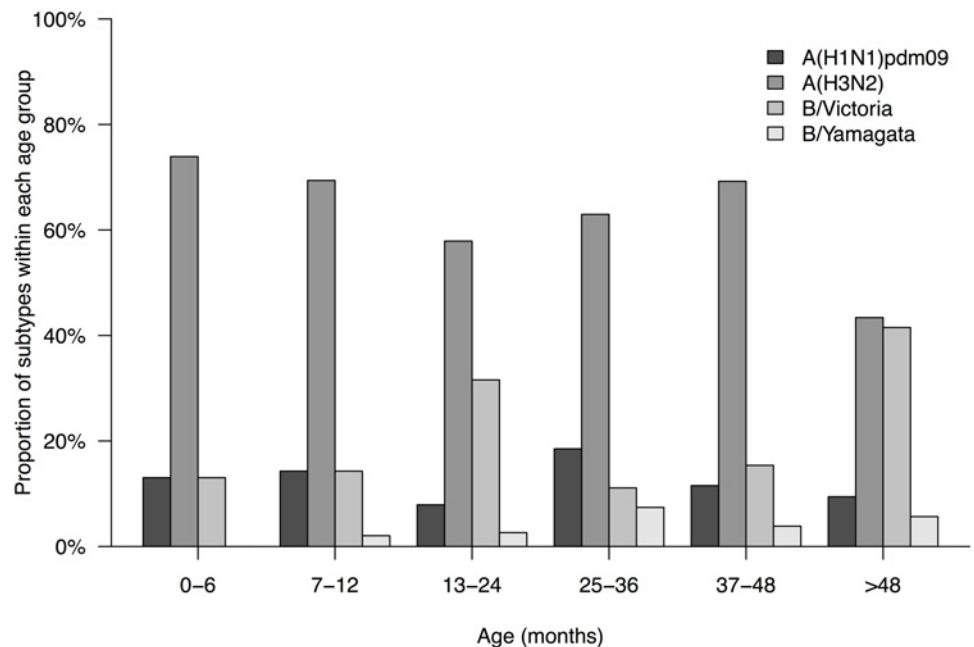


Fig 2. Estimated hospitalization rates (%) attributable to influenza infection by age group and by type/subtype in Guangzhou, China, January, 2010 to December, 2012.

doi:10.1371/journal.pone.0120983.g002

Table 2. Personal history of the studied patients with influenza virus infection.

Factors	A/H1N1pdm09 (n = 26)	A/H3N2 (n = 131)	B (n = 59)	P ¹⁾
Secondhand smoke	10(38.5)	45(34.4)	20(33.9)	0.9912
Caesarean	12(46.2)	58(44.3)	26(44.1)	0.9823
≥1 Underlying condition	6(42.3)	53(40.5)	19(32.2)	0.7917
Prematurity	1(3.8)	8(6.1)	7(11.9)	0.2847
Pulmonary	4(15.4)	15(11.5)	8(13.6)	0.9722
Neurologic	1(3.8)	3(2.3)	1(1.7)	ND
Cardiac	0(0)	2(1.5)	2(3.4)	ND
Renal	1(3.8)	1(0.8)	0(0)	ND

Data are shown as number (%)

¹⁾ Comparisons were made using Fisher's exact test for categorical variables.

ND: Not determined

doi:10.1371/journal.pone.0120983.t002

The recurrence of H1N1pdm09 was observed during the first half of 2011 and was then replaced by influenza B. In 2012, influenza A H3N2 and influenza B were found to be the major subtypes co-circulating in the population. In general, influenza activity peaked in the spring during the three years. A similar circulation pattern of influenza subtypes in hospitalized children was observed in the central China and Hong Kong in the post-pandemic period when compared to our findings [7,8]. Taken together, our results contribute to a deeper understanding of the prevalence of influenza subtypes in the southern China.

Numerous studies have investigated the age distribution of hospitalized patients who were infected by pandemic and seasonal influenza viruses after the pandemic period [8, 13–16]. Our study focuses on understanding the attack age group of different influenza subtypes in hospitalized children who were suffered from relatively respiratory illness (mainly pneumonia or acute bronchitis) and correlate to the clinical manifestation. A higher mean age was observed from the group of influenza B infection (B: 45.0 months vs H1N1pdm09: 34.4 months vs H3N2: 32.5 months) and a large proportion (>47%) of influenza B virus infected children in our study were older than 48 months. Our findings are consistent to several studies that children with influenza B are usually older than those with influenza A and a close mean age between patients with H1N1pdm09 and seasonal influenza A infection [14, 17–19]. Interestingly, a downward-shift in age distribution was found in the hospitalized children infected by H1N1pdm09, H3N2 or influenza B virus in central China. Different outcomes from the two location of China may associate to the climates, diet or other environmental factors.

Although we have found quite high numbers of patients with gastrointestinal symptoms among the three groups, no difference of any clinical presentation and duration of hospitalization between the infection groups by H1N1pdm09, H3N2 and influenza B viruses was observed. It has been reported that children in Nicaragua had a higher clinical attack rate of H1N1pdm09 compared to the group of seasonal influenza A/B viruses during the pandemic period [20]. The group of H1N1pdm09 showed more symptoms of lower respiratory infection and gastrointestinal symptoms than those who were infected by seasonal influenza viruses. However, an age-matched comparison study from Hong Kong demonstrated that there was no difference in most of the clinical presentation including the gastrointestinal symptoms between the hospitalized children infected by the pandemic and seasonal subtypes [13]. Similar studies have also been done during the post pandemic phase in Athens that the clinical presentation was similar between the children who were infected by the pandemic or seasonal influenza viruses [14]. However, a shorter mean length of hospitalization from the pandemic H1N1 group

was observed in the same study. It could be due to the fact that 97% of the patients infected by H1N1pdm09 virus in the study had received oseltamivir while none of the patients in the seasonal cohort received antivirals. On the other hand, there is no routine antiviral therapy such as oseltamivir given to the patients with similar clinical presentation in China. Although study showed that having an underlying neurologic disorder is a risk factor for admission to the ICU with influenza A (H1N1) pdm09 [21], similar association was not found in our study which may be due to the limited numbers of related cases.

Interestingly, a high percentage of cases with co-infection of mycoplasma pneumoniae were commonly found in all of our study groups. This finding may be associated with the fact that mycoplasma pneumoniae is one of the common pathogens to cause community-acquired respiratory infections and atypical pneumonia [22]. It has been reported that prevalence of this pathogen in children reached to 24.65% in China [23]. However, whether the co-infection of influenza viruses may enhance the pathogenicity during the infection is still needed to be further investigated. While in developed countries, the bacterial co-infection rate reaches up to approximately 28%, only very limited cases from this study were identified as bacterial co-infection [24]. It may be due to the difference in clinical practice on frequent use of antibiotics in China.

There are some limitations in this study. Firstly, our study did not conduct in all hospitals in Guangzhou city. Although our hospital is one of the biggest respiratory disease hospitals in Guangzhou, we have not enough data to estimate the total number of influenza virus infected cases among the whole city. Secondly, throat swabs instead of nasopharyngeal swabs were collected and used to detect influenza infection in this study. Our detection may not fully cover all the positive patients whose infection mainly localized at the upper respiratory tract. Thirdly, the patients screening in this study is based on the definition of LRTI but not SARI although there are only slight differences between them.

In conclusion, higher infection rate of seasonal H3N2 was found in hospitalized children with LRTI than with pdm09 H1N1 and influenza B infection. The severity of the infections was generally mild and no difference in the clinical presentation among the three subtypes was observed. The mycoplasma pneumoniae but not bacterial co-infections were commonly found in our cases.

Supporting Information

S1 Dataset. Raw Dataset of the study.
(XLSX)

Acknowledgments

We thank Horace Lee for the technical support.

Author Contributions

Conceived and designed the experiments: WDG XYG ZFY DHC. Performed the experiments: WDG XYG TTC SGW SHP. Analyzed the data: WDG XYG CKPM BJC ZFY DHC. Contributed reagents/materials/analysis tools: ZFY DHC. Wrote the paper: WDG XYG CKPM ZFY DHC.

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