Virologically Confirmed Population-Based Burden of Hospitalization Caused by Influenza A and B among Children in Hong Kong

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(See the editorial commentary by Edwards, on pages 1022–4.)

Background. We sought to determine the virologically confirmed hospitalization rates associated with influenza virus infection among Hong Kong children.

Methods. Patients <18 years of age who lived on Hong Kong Island (a separate island within Hong Kong) and were admitted to either of the only 2 public hospitals on the island for a febrile acute respiratory infection on 1 fixed day of the week in each hospital from October 2003 through September 2006 were prospectively recruited. These 2 hospitals together accounted for 72.5% of all general pediatric admissions in Hong Kong Island with a known population denominator. Nasopharyngeal aspirates were obtained from all recruited patients and were tested for influenza A and influenza B viruses by direct antigen detection and culture.

Results. All cases of influenza A during 2003–2004 were caused by H3N2 virus, whereas 85.7% of cases during 2004–2005 were due to H3N2 virus, and 93.5% during 2005–2006 were due to H1N1 virus. During 2004–2005, infants <1 year of age had the highest rate of hospitalization for influenza A (103.8 cases per 10,000 population), whereas children 1 year of age had the highest rate of hospitalization during the other 2 seasons (95.5 and 54.6 cases per 10,000 population during 2003–2004 and 2005–2006, respectively). A protection rate of 25%, presumably attributable to maternal antibodies, was seen in infants <1 year of age who were hospitalized during 2003–2004 with infection due to an H3N2 virus that had been in circulation. The hospitalization rates for influenza B were highest among children 2–4 years of age.

Conclusions. This population-based study of hospitalizations due to virologically confirmed influenza demonstrated a very high burden of disease among young children in Hong Kong. The morbidity varied with virus type, subtype, and antigenic variants.

Accurate data on the disease burden associated with seasonal influenza are important to inform the formulation of immunization and other public health policies and in assessing the possible impact of future pandemics. Statistical models that estimate excess mortality above that of the expected seasonal variations have limitations of confounding by causes or infections (eg,

respiratory syntactical virus) other than influenza [1–7]. Furthermore, such methods are not easily applied in tropical and subtropical regions, where influenza seasonality is variable and spread over many months of the year. A retrospective, population-based study that used modeling of excess hospitalization estimated high influenza hospitalization rates among children in Hong Kong [8]. There was good separation of influenza activities from that of respiratory syntactical virus in 2 of the 3 study years, and intensive virologic investigation in 1 study hospital improved the estimation of disease burden. Alternatively, a Thai study extrapolated hospitalization for clinically defined influenza pneumonia associated with virologic confirmation in a few intensively studied hospitals to the larger population [9]. However, both approaches still provided estimates,

rather than actual virologically confirmed hospitalization data.

Therefore, we conducted a prospective 3-year virological study of a systematic sample of all pediatric hospitalizations associated with acute respiratory infection in the only 2 public hospitals on Hong Kong Island, which account for 72.5% of all hospital care on the island. Instead of using models of estimation, this study provided exact documentation of children hospitalized for influenza infection at a population level. We report here the findings of the first 3 years of the study, 2003–2006.

PATIENTS AND METHODS

Hong Kong Special Administrative Region is made up of Hong Kong Island, the Kowloon peninsula, the New Territories, and some sparsely populated outlying islands. In 2006, the population of persons <18 years of age who resided in Hong Kong Island was 195,922 [10]. Pamela Youde Nethersole Eastern Hospital (PYNEH), which is situated at the eastern end of the island, and Queen Mary Hospital (QMH), which is situated at the southwestern end of the island, are the only 2 public hospitals on Hong Kong Island, with a total of 153 pediatric beds; these hospitals account for 72.5% of all pediatric hospital admissions, according to Hong Kong Special Administrative Region Government statistics [11]. Although Hong Kong Island is not an entirely closed community, parents from Kowloon or the New Territories rarely bring their children across the Harbor for emergency department attendance or hospitalization for acute general pediatric problems. Therefore, we can relate admission to these 2 hospitals to the population resident in Hong Kong Island. Census data were used to define the age-stratified population at risk.

From October 2003 through September 2006, all patients <18 years of age with a Hong Kong Island home address who were admitted to PYNEH or QMH for a febrile acute respiratory infection, defined as temperature ≥38°C with any respiratory symptom (eg, cough, runny nose, and sorethroat), were recruited during two 24-h periods of the week, 1 day each from PYNEH and QMH. Systematic sampling on 1 day per week was employed because of budget limitations. To avoid the impact and aftermath of the severe acute respiratory syndrome (SARS) outbreak that occurred during March–June 2003, this study started in October 2003. Each study year starts on 1 October and ends on 30 September of the following year. Nasopharyngeal aspirates were obtained from all patients. Detection of influenza A and B viruses was done by direct antigen detection by immunofluorescence and culture at the microbiology laboratory at QMH. Written informed consent was obtained prior to study enrollment.

The calculation of the population <18 years of age who were hospitalized for influenza on Hong Kong Island was made by multiplying the number of hospitalizations for influenza each year by the reciprocal of the proportion of children served by the 2 hospitals (ie, $1 \div 0.725$). With use of the age-stratified population on Hong Kong Island, we calculated the exact rates of hospitalization for influenza for each age group. We also estimated the 95% confidence interval for these hospitalization rates, with the assumption that the hospitalization data was in Poisson distribution.

RESULTS

Seasonality of influenza. The total number pediatric hospital admissions for acute infection for the 2 hospitals were 13,197 (55.1%) in PYNEH and 10,748 (44.9%) in QMH in the 3 years. A total of 1031 subjects (253 during 2003–2004, 368 during 2004–2005, and 410 during 2005–2006) were recruited: 587 (56.9%) from PYNEH and 444 (43.1%) from QMH. Seventy-two (7%) of these 1031 subjects had received influenza vaccination. The mean number of patients admitted to the hospital on the sampling day was not statistically significantly different from the number admitted to the hospital on the nonsampling days (data not shown). Although testing nasopharyngeal aspirates for respiratory viruses is a routine diagnostic procedure for children who are admitted to the hospital with acute respiratory illnesses in QMH and is generally (although not always) used in PYNEH, the 1 day per week setup was to allow intensive monitoring by the research nurse to ensure that all eligible patients were recruited. Therefore, a specimen was obtained from all subjects who fulfilled the inclusion criteria. The seasonality of influenza A and B is shown in Figures 1. The influenza subtypes and antigenic variants that circulated in Hong Kong are shown (Table 1) (W. Lim, unpublished data). In all 3 years, cases of influenza A had a peak during the period from late winter through spring and a peak during summer. There was little influenza B virus activity during 2003–2004. During 2004–2005, the influenza B activity occurred in the spring; during 2005–2006 (when it accounted for 23% of all influenza diagnosis), influenza B virus activity occurred even earlier and coincided with the influenza A virus peak of late winter and spring.

Annual rates of hospitalization due to influenza. Over the 3 years, 102 patients received a diagnosis of influenza A virus infection, and 45 patients received a diagnosis of influenza B virus infection. A total of 87 children had both direct antigen test results and cultures positive for influenza A virus, and 24 children had both direct antigen test results and cultures positive for influenza B virus. Six patients received a diagnosis of influenza A and 2 patients received a diagnosis of influenza B on the basis of direct antigen test results alone, and 9 patients received a diagnosis of influenza A and 19 received a diagnosis of influenza B on the basis of culture results alone. One specimen was insufficient for direct antigen testing but had cultures that were positive for influenza B virus. The rates of hospital-
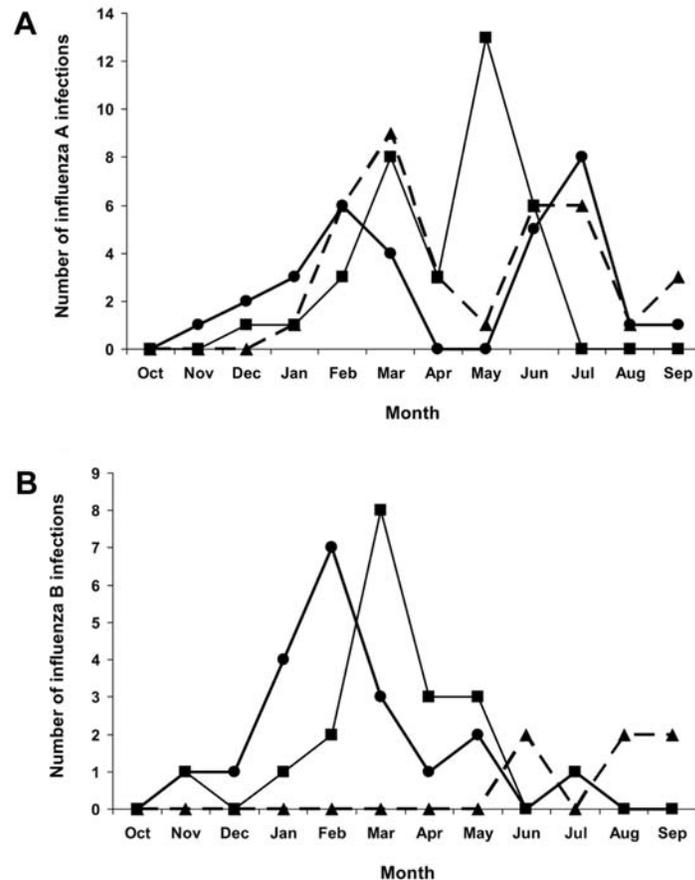
Figure 1. Seasonality of influenza A *(A)* and influenza B *(B)* during 2003–2004 *(triangles)*, 2004–2005 *(squares)*, and 2005–2006 *(circles)*.

ization for influenza virus infection among the overall population of children on Hong Kong Island during 2003–2004, 2004–2005, and 2005–2006 was extrapolated from this virologically confirmed data (Table 2). The highest rates of hospitalization for influenza A were among children <2 years of age, whereas the highest rate of hospitalization for influenza B were among children 2–4 years of age. During the 2004–2005 season, when a novel drift variant of H3N2 appeared, the highest rate of hospitalization was among infants who were <1 year of age. In contrast, during 2003–2004 and 2005–2006, children who were 1 year of age had the highest rate of hospitalization for influenza A virus infection; infection due to subtype H3N2 predominated during the 2003–2004 season, and infection due to subtype H1N1 predominated during the 2005–2006 season. Hospitalization rates among infants <6 months of age could not be calculated, because the population denominator was only available in yearly age groups. However, 6 (75%) of 8 infants <12 months of age who were hospitalized for H3N2 infection during 2004–2005, when there was an antigenic variant, were ≤6 months of age, compared with 1 (16.6%) of 6 during 2003–2004, when the H3 virus had been antigenically similar to the virus from the previous season. None of infants

<12 months of age who were hospitalized for H1N1 virus infection were ≤6 months of age. Remarkably, no infants <12 months of age were hospitalized with influenza B in any year, and no children aged 1–2 years of age were hospitalized during 2003–2004 or 2005–2006. In contrast with influenza A, rates of hospitalization due to influenza B were highest among children 2-4 years of age in all 3 years of the study.

DISCUSSION

Many studies use mathematical models or extrapolation to estimate influenza disease burden [1, 8, 12–18]. Elegant laboratory-confirmed surveillance studies in populations in the United States have also documented influenza disease over the decades [5, 6, 19–23]. Here, we used virologically confirmed diagnoses in a systematic sample covering 72.5% of all hospitalizations in the population under investigation to document the exact childhood hospitalization disease burden associated with influenza virus infection in the total population of this geographically defined community in Hong Kong.

The rates of hospitalization for influenza viruses changed from year to year over the 3 study years. The highest rates of

Table 1. Influenza Strains and Subtypes in Circulation during the Study Years

Year	No. of isolates	Percentatge of isolates		
		H3N2 virus	H1N1 virus	Influenza B virus
2003–2004	4938	93.6 (A/Fujian/411/02-like)	0.5 (A/New Caledonia/20/99-like)	5.9 (Victoria/2/87-like and Yamagata/16/88-like)
2004–2005	5733	77.8 (A/California/7/04-like[a])	6.5 (A/New Caledonia/20/99-like)	15.7 (Yamagata/16/88-like)
2005–2006	3956	4.9 (A/California/7/04-like)	71.8 (A/New Caledonia/20/99-like and A/HK/2652/06-like[a])	23.3 (Victoria/2/87-like)

[a] New circulating strain.

hospitalization in the youngest age group (<1 year) occurred during 2004–2005 (103.8 cases per 10,000 population) when a novel antigenic variant of H3N2 (A/California/7/2004-like) emerged, with the lowest hospitalization rate (38.9 cases per 10,000 population) during 2005–2006, a season with predominantly H1N1 and influenza B activity. The age-specific incidences of influenza-related hospitalization documented here for a largely unvaccinated population were higher than that estimated from most recent studies from Canada, Germany, Spain, and the United States [12–18]. An early prospective population-based surveillance of hospitalization of US children <5 years of age in Monroe County, New York, and Davidson County, Tennessee, under the New Vaccine Surveillance Network documented rather low rates of influenza hospitalization: 24 cases per 10,000 children 0–5 months of age, or 6 cases per 10,000 population overall [24]. However, that study had enrollment rates of eligible patients that ranged from 15% to 69% in different age groups and only covered 1 year during which H1N1 and influenza B virus were in circulation. A follow-up study that encompassed Nashville, Tennessee; Rochester, Minnesota; and Cincinnati, Ohio, was conducted during 2000–2004 [25]. The rate of 77.8 cases per 10,000 population in the group of children <1 year of age during 2003–2004 in Hong Kong was comparable to the hospitalization rates of 72 cases per 10,000 population in infants <6 months for the same season in this US study with laboratory-confirmation. However, the 95.5 cases per 10,000 population in children 1 year of age was much higher than the 15 cases per 10,000 children 6–23 months of age in the United States. As seen in this study, the US study also demonstrated a 3-fold difference in hospitalization rates in the youngest age group from year to year. The rates of influenza vaccination in the US study ranged from 11% to 23% in the latter years of the study among all children with acute respiratory infection. This considerably higher vaccination rate may partially explain the rate difference seen between the 2 studies. There were also methodologic differences between the 2 studies. Polymerase chain reaction (PCR) was used for diagnosis in the US studies but was not used in this study, which may lead to an underestimation of the disease burden in Hong Kong. The hospitalization rates documented here were, in general, only slightly higher than those reported in another 25-year pro-

spective study involving US children <5 years of age who were followed up in the Vanderbilt Vaccine Clinic, which documented an annual rate of 30–40 cases per 10,000 children <2 years of age by culture of nasal wash specimens [26].

Infants, especially those <6 months of age, have been documented to have the highest rates of hospitalization and mortality associated with influenza [5, 8, 14, 15, 20, 21]. This was not seen in our study during the 2003–2004 and 2005–2006 seasons. Moreover, the rate of hospitalization for H3N2 infection among infants <1 year of age during 2003–2004 (77.8 cases per 10,000 population) was 25% lower than that during the following year (90.8 cases per 10,000 population). H3N2 influenza A/Fujian 02–like viruses had been in circulation in Hong Kong, and we postulate that the lower hospitalization rates among these infants during 2003–2004 was attributable to protective maternal antibodies from mothers who might have encountered the virus during the previous year. This was further supported by the observation that infants ≤6 months of age accounted for only 16.7% of infants <12 months of age who were hospitalized during 2003–2004 but accounted for 85% of infants <12 months of age who were hospitalized during 2004–2005. The antigenically drifted H3N2 strain that emerged in 2004–2005 would result in less protection from maternal antibody. Maternal antibodies also likely accounted for the lower hospitalization rate among infants <1 year of age, compared with that among infants 1 year of age, during 2005–2006. The dominant strain that year was H1N1 A/New Caledonia, which had been in circulation since 2001, whereas the antigenically distinct A/HK/2652/06-like viruses did not start circulating until mid-May 2006, with limited impact on this age group during the study period that ended in September 2006. In fact, no infant ≤6 months of age was hospitalized for influenza A during 2005–2006 in this study. Glezen et al [18] have also documented that infants experienced fewer influenza infections during the first 6 months of life than during the second 6 months of life. Protection from maternal antibodies was also evidenced by a recent randomized study which showed that maternal influenza vaccination provided 63% effectiveness in preventing laboratory-confirmed influenza in infants up to 6 months of age [27].

The hospitalization rate among children 1 year of age during

Table 2. Age-Stratified Rates of Hospitalization for Influenza Virus Infection among Children on Hong Kong Island

Age, years	Population at risk	2003–2004				2004–2005				2005–2006			
		Influenza A virus			Influenza B virus	Influenza A virus			Influenza B virus	Influenza A virus			Influenza B virus
		Overall	H3N2	H1N1		Overall	H3N2	H1N1		Overall	H3N2	H1N1	
<1	7447	77.8 (62–97)	77.8	0	0	103.8 (84–126)	90.8	13.0	0	38.9 (28–54)	0	38.9	0
1	7078	95.5 (78–117)	95.5	0	0	40.9 (29–56)	40.9	0	27.3 (18–39)	54.6 (41–72)	0	54.6	0
2–4	22,818	59.5 (46–77)	59.2	0	8.5 (4–17)	42.3 (30–56)	38.1	4.2	42.3 (30–56)	38.1 (27–52)	0	38.1	25.4 (16–37)
5–9	53,094	10.9 (5–20)	10.9	0	7.3 (3–14)	21.9 (14–33)	16.4	5.5	7.3 (3–14)	18.2 (11–28)	0	18.2	16.4 (9–26)
10–14	65,838	2.9 (0.6–8.7)	2.9	0	0	1.5 (0.02–5.6)	1.5	0	2.9 (0.6–8.7)	2.9 (0.6–8.7)	0	2.9	5.9 (2.2–13.1)
15–17	39,647	2.4 (0.2–7.2)	2.4	0	0	2.4 (0.2–7.2)	2.4	0	2.4 (0.2–7.2)	4.8 (1.6–11.6)	2.4	2.4	2.4 (0.2–7.2)

NOTE. Data are no. of cases per 10,000 population or no. of cases per 10,000 population (95% confidence interval), unless otherwise indicated.

2003–2004 was higher than that among the younger age group and was twice the hospitalization rate among the same age group in the following season. We postulate the accumulation of susceptible individuals in that age group as an explanation for this phenomenon. The SARS epidemic occurred from March through June 2003 in Hong Kong. It has been suggested that the nonpharmaceutical interventions and social distancing measures implemented during this period led to a reduction in the circulation of all respiratory viruses, including influenza viruses, in Hong Kong [28]. This might have resulted in a cohort of young children who were less affected by influenza in 2003 and were therefore more vulnerable to influenza during the 2003–2004 season. An alternative explanation is the accumulation of an increased number of susceptible children 1–2 years of age who had been more efficiently protected by maternal antibodies during the previous 2002–2003 influenza season with a nondrifted virus, thereby rendering them fully susceptible during the following year, when maternal antibodies waned. The hospitalization rate for children 1 year of age was also the higher than that for other age groups during 2005–2006: 75% of children 1 year of age who were hospitalized due to influenza were hospitalized in July 2006, after the new A/HK virus started to circulate in May 2006.

In contrast with influenza A, hospitalization rates for influenza B were consistently highest in the group of children 2–4 years of age in all 3 study years, with no cases requiring hospitalization in the group of infants <1 year of age. This lack of hospitalization among young infants is surprising and, to our knowledge, has not been reported elsewhere. Other studies have shown that children infected with influenza B virus were older than those infected with influenza A virus [29, 30]. Influenza B/Victoria and B/Yamagata viruses are 2 antigenically and genetically distinct lineages of influenza B virus that have cocirculated among humans since 1983 [26]. The general adult population is likely to be immune to both strains. The group of infants <1 year of age could have benefited from protection from maternal antibodies. There was also no hospitalization for the group of children 1 year of age in 2 of the 3 study years. In 2004–2005, when the hospitalization rate among children

2–4 years of age was high, we documented hospitalization in the group of children 1 year of age, as well, but this was not seen in the following year.

The rates of hospitalization for influenza virus infection documented during the 3 study years were significantly lower than that of >200 cases per 10,000 population among children <2 year of age, documented in our previous study [8]. However, there was only a 1.1–1.8-fold difference between mean hospitalization rates for the older age groups between the 2 studies. Influenza circulation is dynamic, and so is the burden of influenza disease. One limitation of this present study is that diagnosis of influenza virus infection was made without PCR. In another study involving a different cohort, we found that 11% of all children with influenza A virus infection had infections that were detected by PCR alone, whereas no child had influenza B virus infection detected by PCR only (unpublished data). Despite the likelihood that hospitalization rates of influenza A infection reported here may be underestimated by ~11%, this does not explain the difference between data reported in this study and that reported in our previous study, because PCR was also not used in the 1997–1999 study [8]. Another limitation is that young infants with influenza may present with fever alone, without significant respiratory complaints [25]. Our recruitment criteria may underestimate the hospitalization rates among this group of infants. Possible explanations for variation of documented hospitalization disease burden include the impact of antigenic drift. For example, 1997–1998 saw the introduction of a major antigenic drift variant, A/Syndey/5/097, whereas during the 2003–2004 season, the virus strains were not as markedly different from those present in previous years. During 2005–2006, H1N1 and influenza B virus, rather than H3N2 virus, dominated. Finally, the experience with SARS may have made the population of Hong Kong more vigilant and led to better personal hygiene, which may have reduced the amount of virus transmission. Alternatively, these discrepancies may arise from inaccuracies inherent in the models used, especially in tropical contexts.

In summary, by using systematic sampling of all patients admitted to pediatric hospitals with acute respiratory diseases,

we have established an accurate hospitalization burden caused by influenza, have documented definitively very high hospitalization rates associated with influenza virus infection in young children in Hong Kong, and have demonstrated potential protection from maternal antibodies. More widespread use of influenza vaccine in children should be considered in Hong Kong.

Acknowledgments

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