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INFLUENZA-RELATED HOSPITALIZATIONS AMONG CHILDREN IN HONG KONG

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ABSTRACT

Background It has been difficult to define the burden of influenza in children because of confounding by the cocirculation of respiratory syncytial virus (RSV). In Hong Kong, China, the influenza and RSV infection seasons sometimes do not overlap, thus providing an opportunity to estimate the rate of influenza-related hospitalization in a defined population, free from the effects of RSV.

Methods In a retrospective, population-based study, we estimated the influenza-associated excess rate of hospitalization among children 15 years old or younger in the Hong Kong Special Administrative Region from 1997 to 1999. Data from a single hospital with intensive use of virologic analyses for diagnosis were obtained to define and adjust for underestimation of the model.

Results Peaks of influenza and RSV infection activity were well separated in 1998 and 1999 but overlapped in 1997. The adjusted rates of excess hospitalization for acute respiratory disease that were attributable to influenza were 278.5 and 288.2 per 10,000 children less than 1 year of age in 1998 and 1999, respectively; 218.4 and 209.3 per 10,000 children 1 to less than 2 years of age; 125.6 and 77.3 per 10,000 children 2 to less than 5 years of age; 57.3 and 20.9 per 10,000 children 5 to less than 10 years of age; and 16.4 and 8.1 per 10,000 children 10 to 15 years of age.

Conclusions In the subtropics, influenza is an important cause of hospitalization among children, with rates exceeding those reported for temperate regions. (N Engl J Med 2002;347:2097-103.)

THE Hong Kong Special Administrative Region of China is situated within the hypothetical epicenter of influenza pandemics and serves as a sentinel post for the region.[1,2] Although the influenza A H5N1 virus epidemic in 1997 received much attention, the usual annual epidemics of influenza are generally believed to be clinically insignificant in Hong Kong as well as other tropical and subtropical regions.[3-7] The importance of defining the disease burden associated with influenza has been recognized.[8]

During epidemics in temperate regions, influenza affects 30 to 40 percent of children.[9,10] Although the effect of influenza on children with underlying medical conditions is well recognized, its effect on healthy children is less clear.[11] In the United States, respiratory syncytial virus (RSV) circulates with influenzavirus during winter, making it difficult to separate their clinical effects in the population.[12-15] Recent studies have attempted to separate the roles of influenzavirus and RSV by estimating the increase in morbidity associated with periods during which influenza predominated.[16,17] However, considerable uncertainty remains as to whether influenza was responsible for all, or even most, of the excess morbidity.[18]

RSV infection occurs in summer in Hong Kong, whereas the influenza season varies from year to year. In some years, the influenza season overlaps that of RSV infection, whereas in others it has a sharp peak in spring that separates it from RSV infections. Ninety percent of all the hospitalizations in Hong Kong involve hospitals within the Hospital Authority of the Hong Kong Special Administrative Region. We as-

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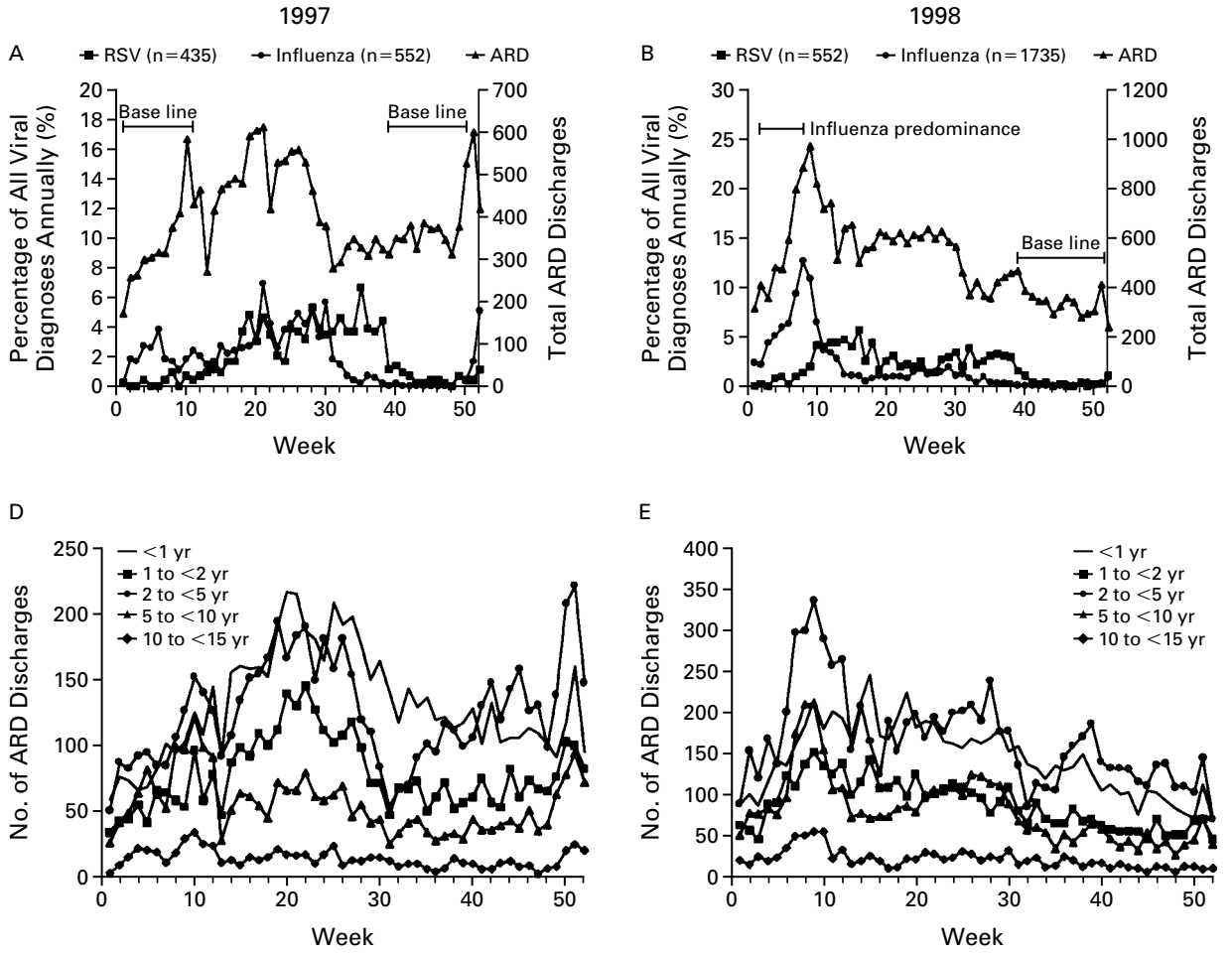


Figure 1. Correlation between the Number of Laboratory Diagnoses of Influenza and Respiratory Syncytial Virus (RSV), Expressed as a Percentage of All Viral Diagnoses Annually, at Queen Mary Hospital and the Number of Discharge Diagnoses of Acute Respiratory Disease (ARD) at Hospital Authority Hospitals in Hong Kong in 1997 (Panel A), 1998 (Panel B), and 1999 (Panel C), and the Number of Diagnoses of Acute Respiratory Disease According to Age in 1997 (Panel D), 1998 (Panel E), and 1999 (Panel F).

The total numbers of cases of influenza diagnosed at the Queen Mary Hospital virology laboratory for the whole of Hong Kong Island for the years 1997, 1998, and 1999 were 552, 1735, and 562, respectively. The numbers of RSV infections diagnosed in the same years were 435, 562, and 718, respectively. The periods in which influenza predominated and the base-line periods of influenza and RSV infection activity are shown. In 1997, there was no definable period in which influenza predominated.

sessed the effect of influenza in a well-defined population in Hong Kong, after adjustment for the confounding influence of RSV.

METHODS

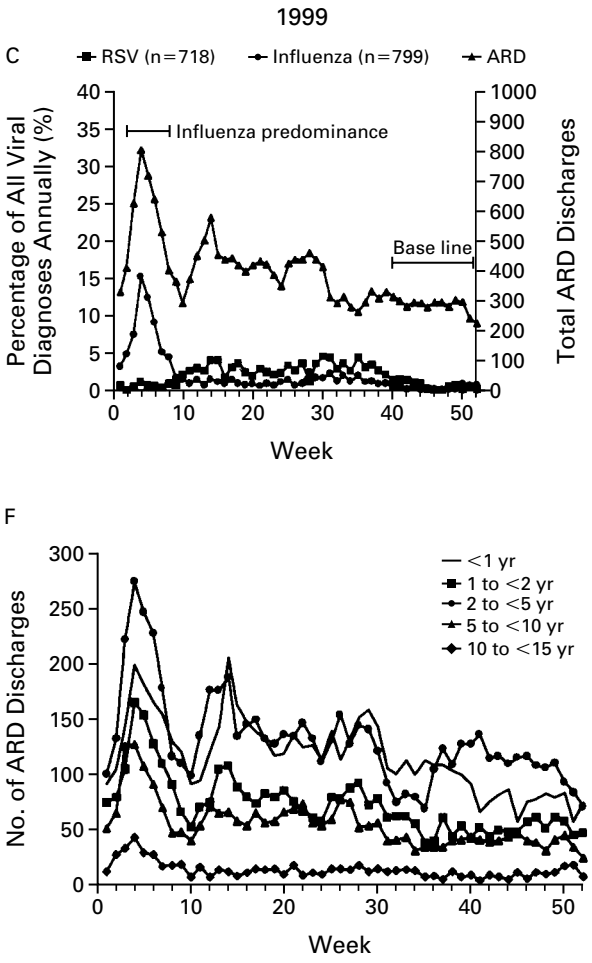
Study Design

We performed a retrospective population-based study of children who were 15 years old or younger to determine rates of hospitalization for acute respiratory disease associated with influenza. We compared mean hospitalization rates during periods of high influenza activity and low RSV activity (influenza-predominant periods) with those during which both influenza and RSV activity were low (base line). The same approach was applied to a single hospital — Queen Mary Hospital — where intensive virologic investigation of respiratory tract infections was routine. Data on the excess rate of hospitalizations attributable to influenza at Queen Mary Hospital were compared with the numbers of patients with laboratory-diagnosed influenza.

Population and Medical Data

Hong Kong occupies an area of 1076 km^2 and had a population of 6,865,600 as of 1999. Though situated within the tropics, it has a subtropical climate. The hospital authority manages a total of 28,517 hospital beds and accounts for 90 percent of all hospital admissions in the Hong Kong Special Administrative Region. Census data were used to define the population at risk. Hospital Authority hospitals served an estimated 1,057,500 of the 1,175,000 children who were 15 years of age or younger.

Since 1995, all Hospital Authority inpatient data, including dem-



ographic characteristics, dates of admission and discharge, diagnoses, and procedures, have been stored in a central computerized data base. We obtained data stripped of identifiers on children who were 15 years of age or younger and who were given a discharge diagnosis of acute respiratory disease (codes 460 to 466 or 480 to 487 of the *International Classification of Diseases, 9th Revision, Clinical Modification* [ICD-9-CM]) from all Hospital Authority hospitals from January 1997 to December 1999. Data for each record included up to four discharge diagnoses in addition to the code for acute respiratory disease, age, sex, dates of admission and discharge, and vital status. We also obtained from each record the following diagnostic codes for underlying conditions that increase the risk of an adverse outcome after influenza according to the Advisory Committee for Immunization Practices: congenital and other cardiac diseases (ICD-9-CM codes 093, 391, 393 to 398, 410 to 417, 428, 429, and 745 to 747.4), bronchopulmonary dysplasia (ICD-9-CM code 770.7), asthma (ICD-9-CM code 493), diabetes mellitus (ICD-9-CM code 250), human immunodeficiency virus infection (ICD-9-CM codes 042 to 044 and 136.3), cancer (ICD-9-CM codes 140 to 172 and 174 to 208.9), and chronic renal disease (ICD-9-CM codes 581 to 583, 585, and 587).

Definition of Study Periods

Viral activity was defined on the basis of the numbers of virologically confirmed infections with influenzavirus A and influenzavirus B, RSV, parainfluenzavirus, and adenovirus recorded each week by the virology laboratory of Queen Mary Hospital. Each year this laboratory receives 6000 to 7000 nasopharyngeal aspirates for the diagnosis of infections with respiratory virus by antigen detection and cultures of samples obtained from hospitals on Hong Kong Island. Given the small size of the Hong Kong Special Administrative Region, we assumed that the pattern of viral activity reflected by the data of the virology laboratory is representative of the regional pattern. Data on the types and subtypes of influenzavirus circulating in Hong Kong in the years 1997 through 1999 were obtained from the Department of Health.[19]

The period in which influenza predominated was arbitrarily defined as a period of two or more consecutive weeks in which at least 4 percent of the annual number of virologically confirmed influenza diagnoses were recorded and less than 2 percent of the annual number of RSV infections were diagnosed. For comparison, periods of at least two consecutive weeks in which both the numbers of RSV infection and influenza diagnoses were less than 2 percent of the annual total were defined as periods of base-line activity for both viruses.

Statistical Analysis

The number of children 15 years of age or younger who were hospitalized with acute respiratory disease in Hospital Authority hospitals was calculated according to age group. The estimate for the Hong Kong Special Administrative Region was made by multiplying the number of hospitalizations for acute respiratory disease in Hospital Authority hospitals by the reciprocal of the proportion of children served (e.g., $1 \div 0.9$). For each age group, we calculated the excess rates of hospitalization attributable to influenza by subtracting the rates of hospitalization during base-line periods from the rate during the period in which influenza predominated. The duration of hospitalization was based on the dates of admission and discharge.

We conducted a similar analysis of data from a single hospital (Queen Mary Hospital) and compared the estimated excess number of influenza-associated hospitalizations with the total number of virologically confirmed diagnoses of influenza. We determined the degree of underestimation inherent in this model and corrected the data from the whole of the Hong Kong Special Administrative Region to derive age-adjusted rates of hospitalization.

RESULTS

The seasonal pattern of influenza and RSV infections and that of inpatient discharges for acute respiratory disease in Hospital Authority hospitals are shown in Figure 1. In 1998 and 1999, the peaks of influenza and RSV activity were distinct, whereas in 1997 there was considerable overlap between the two. In 1998 and 1999, the peak incidence of hospitalization for acute respiratory disease clearly coincided with the peak periods of influenza activity. This relation was discernible in all age groups up to the age of 10 years.

Influenza A subtype H3N2 and influenza B, respectively, accounted for 65 percent and 27 percent of all laboratory-proved diagnoses of influenza in 1997; 94 percent and 5 percent, respectively, in 1998; and 83 percent and 17 percent, respectively, in 1999. Influenza A subtype H1N1 accounted for the remainder, except in 1997, when infections with subtype H5N1 accounted for 1.9 percent of all diagnoses of influenza.[19]

Periods in Which Influenza Predominated

In both 1998 and 1999, there were seven weeks in which influenza predominated, whereas there were

none in 1997. During the periods in which influenza predominated in 1998 and 1999, there were 4555 and 4242 discharge diagnoses of acute respiratory disease, respectively. In 1997, 1998, and 1999, there were 22, 16, and 13 weeks, respectively, when neither influenzavirus nor RSV was active (base-line periods) (Fig. 1).

During the period in 1998 in which influenza predominated, the average number of virologic diagnoses of influenza, RSV, adenovirus infection, and parainfluenza made per week at the Queen Mary Hospital virology laboratory were 134.7, 4.7, 2.0, and 5.1, respectively. The corresponding averages during the base-line period were 5.1, 2.8, 4.5, and 5.6 per week. Similarly, during 1999, the average numbers of diagnoses of influenza, RSV, adenovirus infection, and parainfluenza were 66.3, 4.0, 4.7, and 5.4, respectively, during the period in which influenza predominated and 2.2, 4.2, 4.7, and 8.9, respectively, during the base-line period. Thus, during 1998 and 1999, the number of diagnoses of infections with respiratory viruses other than influenzavirus during the periods in which influenza predominated and during the base-line periods was similar.

Hospital Rates during Periods in Which Influenza Predominated

The weekly hospitalization rates for acute respiratory disease among children during periods in which influenza predominated and during base-line periods in 1997, 1998, and 1999 are shown in Table 1. In 1997, there was no definable period in which influenza predominated. Among the children discharged during periods in which influenza predominated in 1998 and 1999, 157 (3.4 percent) and 120 (2.8 percent), respectively, had an ICD-9-CM code for one or more underlying conditions that increase the risk of an adverse outcome after influenza. Asthma was the most common underlying condition, accounting for 63 to 72 percent of such high-risk underlying conditions.

There were two deaths associated with acute respiratory disease (from pneumonia and respiratory failure or shock) during each of the seven-week periods in 1998 and 1999 in which influenza predominated. In comparison, there were seven such deaths during the 16 weeks of base-line activity in 1998 and two deaths during the 13 weeks of base-line activity in 1999.

Analysis of the Subpopulation at a Single Hospital

Virologic analyses are routine in all children who are admitted to Queen Mary Hospital with respiratory syndromes suggestive of a viral cause. Of 11,384 acute admissions to the general pediatric wards at Queen Mary Hospital in 1997, 1998, and 1999, a nasopharyngeal aspirate was sent for viral investigation in the case of 8460 (74.0 percent) (Table 2). Applying the excess-hospitalization model to the discharge data from Queen Mary Hospital in 1997, 1998, and 1999 yields estimates of 0, 135.8, and 116.2 excess hospitalizations attributable to influenza, respectively. However, the numbers of children with a virologically confirmed diagnosis of influenza at this hospital in 1997, 1998, and 1999, were 346, 528, and 268, respectively (Table 2). Thus, the method underestimated the true burden of influenza-associated hospitalization by a factor of 3.9 in 1998 and 2.3 in 1999. These values were then applied to the data from the Hong Kong Special Administrative Region, to derive an adjusted estimate of the rates of hospitalization for acute respiratory disease (Table 3).

Annual Rates of Hospitalization for Acute Respiratory Disease Attributable to Influenza

When we extrapolated our adjusted findings to the population of children in the Hong Kong Special Ad-

TABLE 1. RATES OF HOSPITALIZATION FOR ACUTE RESPIRATORY DISEASES AMONG CHILDREN DURING PERIODS IN WHICH INFLUENZA PREDOMINATED AND DURING BASE-LINE PERIODS IN WHICH NEITHER INFLUENZA NOR RESPIRATORY SYNCYTIAL VIRUS INFECTION PREDOMINATED.*

AGE	POPULATION AT RISK	1997		1998		1999	
		INFLUENZA PREDOMINANT	BASE LINE	INFLUENZA PREDOMINANT	BASE LINE	INFLUENZA PREDOMINANT	BASE LINE
		mean weekly rate/10,000 population (95% CI)					
<1 yr	48,240	Undefined	24.8 (22.6–27.0)	34.2 (25.1–43.3)	24.0 (20.4–27.6)	35.3 (28.6–42.1)	17.4 (16.0–18.9)
1 to <2 yr	58,300	Undefined	12.7 (11.2–14.2)	20.1 (13.9–26.7)	12.1 (10.4–13.8)	22.7 (17.0–28.3)	9.7 (9.0–10.5)
2 to <5 yr	212,700	Undefined	6.5 (5.6–7.3)	11.6 (7.4–15.8)	7.0 (6.1–8.0)	10.4 (7.5–13.2)	5.6 (5.1–6.2)
5 to <10 yr	409,800	Undefined	1.5 (1.1–1.7)	3.6 (2.0–5.2)	1.5 (1.1–1.9)	2.4 (1.7–3.2)	1.1 (1.0–1.2)
10 to 15 yr	444,800	Undefined	0.3 (0.2–0.4)	0.9 (0.6–1.3)	0.3 (0.3–0.4)	0.7 (0.5–0.9)	0.2 (0.2–0.3)

*The population at risk is based on census data from 1999. CI denotes confidence interval.

ministrative Region who were 15 years of age or younger, there were 8366 excess hospital discharges in 1998 and 5471 in 1999. During periods in which influenza predominated, the mean (±SD) duration of hospitalization for acute respiratory disease was 3.1± 5.4 days. For the Hospital Authority, this amounted to a mean of 23,342 and 15,264 extra bed-days for cases of acute respiratory disease attributable to influenza, representing between 5.5 and 8.2 percent of all pediatric bed-days.

DISCUSSION

In 1998 and 1999, influenza activity in the Hong Kong Special Administrative Region was clearly distinct from that of RSV infection, and an apparent increase in the rate of hospitalization for acute respiratory disease was temporally associated with peaks of influenza activity in January and February. On the other hand, influenza activity was more broadly distributed in 1997, overlapping that of RSV infection, and was not associated with peaks in the rates of hospi-

TABLE 2. EXCESS HOSPITALIZATION RATES ATTRIBUTABLE TO INFLUENZA AND LABORATORY-CONFIRMED CASES OF INFLUENZA AT A SINGLE HOSPITAL WITH INTENSIVE USE OF VIROLOGIC DIAGNOSIS.

VARIABLE	1997	1998	1999
No. of acute general admissions of children per year	3869	4016	3499
No. of children with respiratory symptoms (%)*	2949 (76.2)	3071 (76.5)	2440 (69.7)
No. of weeks in which influenza predominated	0	7	7
No. of virologically confirmed admissions for influenza per year	346	528	268
No. of virologically confirmed influenza diagnoses obtained during period in which influenza predominated/total no. of influenza diagnoses per year (%)	0/346	233/528 (44.1)	144/268 (53.7)
No. of admissions for acute respiratory disease per week			
During period in which influenza predominated	0	39	35.4
During base-line period	13.5	19.6	18.8
No. of excess admissions for acute respiratory disease per week attributed to influenza	Undefined	19.4	16.6
Total no. of excess admissions for acute respiratory disease attributed to influenza per year	Undefined	135.8	116.2
Extent to which model underestimated the true burden of influenza-associated hospitalization	—†	3.9	2.3

*All children admitted to Queen Mary Hospital with symptoms of viral respiratory tract infection underwent virologic analysis.

†The absence of a period in which influenza predominated in 1997 results in an inability to estimate the rate of influenza-related hospitalization.

TABLE 3. RATES OF EXCESS HOSPITALIZATION FOR ACUTE RESPIRATORY DISEASES ATTRIBUTABLE TO INFLUENZA IN 1998 AND 1999, ACCORDING TO AGE.*

AGE GROUP	1998			1999		
	MEAN WEEKLY RATE	MEAN ANNUAL RATE	ADJUSTED MEAN ANNUAL RATE†	MEAN WEEKLY RATE	MEAN ANNUAL RATE	ADJUSTED MEAN ANNUAL RATE†
	rate/10,000 population (95% CI)					
<1 yr	10.2 (2.1–18.3)	71.4 (14.7–128.1)	278.5 (57.3–499.6)	17.9 (11.9–24.0)	125.3 (83.3–168.0)	288.2 (191.6–386.4)
1 to <2 yr	8.0 (3.5–13.0)	56.0 (24.5–91.0)	218.4 (95.6–354.9)	13.0 (9.0–16.8)	91.0 (63.0–117.6)	209.3 (144.9–270.5)
2 to <5 yr	4.6 (1.8–7.3)	32.2 (12.6–51.1)	125.6 (49.1–199.3)	4.8 (2.8–6.7)	33.6 (19.6–46.9)	77.3 (45.1–107.9)
5 to <10 yr	2.1 (1.1–3.1)	14.7 (7.7–21.7)	57.3 (30.0–84.6)	1.3 (0.9–1.9)	9.1 (6.3–13.3)	20.9 (14.5–30.6)
10 to 15 yr	0.6 (0.4–0.8)	4.2 (2.8–5.6)	16.4 (10.9–21.8)	0.5 (0.3–0.6)	3.5 (2.1–4.2)	8.1 (4.8–9.7)

*The rate of excess hospitalization for 1997 cannot be estimated because there was no period in which influenza predominated. CI denotes confidence interval.

†The mean annual rates were adjusted for the extent of underestimation (as shown in Table 2): a factor of 3.9 in 1998 and 2.3 in 1999.

talization for acute respiratory disease. This finding suggests that the peaks in the rates of hospitalization for acute respiratory disease in 1998 and 1999 were associated with influenza rather than other factors.

The differences in the rates of hospital admission between the periods in which influenza predominated and base-line periods allowed us to compute the rate of excess hospitalizations attributable to influenza. The rates of diagnoses of acute respiratory disease during the base-line periods were generally similar during the three years. As an independent comparison, we applied the excess-hospitalization model to data from a single hospital in which virologic analysis was intensively used for diagnosis.[20,21] In 1999, the period in which influenza predominated had the highest proportion (53.7 percent) of laboratory-proved influenza diagnoses, and the influenza-associated excess rate of hospitalization provided the closest approximation of the number of laboratory-confirmed diagnoses. However, even this approach resulted in a considerable underestimate (by a factor of 2.3). When the periods of influenza and RSV infection overlap, as they did in 1997, a significant proportion of hospitalizations occur during these overlapping periods and are thus excluded from analyses, resulting in an underestimation of the total burden of influenza. Therefore, the excess-hospitalization strategy is useful for estimating the burden of influenza in years in which RSV infection and influenza seasons are separate but grossly underestimates the true disease burden in years in which there are substantial periods in which both viruses circulate simultaneously. In addition, patients with influenza may be hospitalized for complications other than acute respiratory disease — for example, for febrile seizures.[21] Thus, evaluating the incidence of acute respiratory disease alone underestimates the burden of influenza-related disease.

The estimated ranges of influenza-associated rates of hospitalization among otherwise healthy children in the United States were 49.6 to 103.8 per 10,000 children 0 to 11 months of age in one study and 14.4 to 18.7 per 10,000 children 0 to 23 months of age in another.[11,16,17] The corresponding rates were 0 to 2.5 per 10,000 for children 2 to 4 years of age and 0.8 to 4.1 per 10,000 for children 5 to 17 years of age. These estimates excluded children with high-risk underlying conditions and are therefore not directly comparable to our own. However, we found much higher hospitalization rates in Hong Kong, and the magnitude of difference cannot be explained purely by the inclusion of the patients at high risk. In fact, the influenza-related rates of hospitalization in Hong Kong were even higher than those among high-risk children with acute cardiopulmonary disease in the United States (190 per 10,000 children less than 1 year of age, 80 per 10,000 children 1 to less than 3 years of age) and among patients who were at least 65 years old and had underlying cardiac conditions or pulmonary conditions (50.2 per 10,000 and 87.5 per 10,000, respectively).[11,22,23]

The reasons underlying the apparently greater rates of admission for influenza-related illness among children in Hong Kong remain to be explored. The influenza A H3N2 subtype has been associated with higher morbidity and mortality rates than have other subtypes,[24] but the study by Izurieta and colleagues,[16] as well as our own, was carried out during periods in which H3N2 predominated. The possible effect of the avian influenza epidemic of December 1997 on hospital admissions in Hong Kong needs to be considered. The admission data at Queen Mary Hospital indicate that the variation in the general rates of hospitalization among children during the three years of our study was moderate (Table 2). The apparent increase in the rate in 1998 may, in fact, be related more closely to the emergence of a new H3N2 variant (A/Sydney/05/97) in Hong Kong in 1998.

Hospitalization practices in Hong Kong may differ from those in the United States, and it is likely that the threshold for the hospitalization of children is lower. However, we examined excess rates of hospitalization, as did some U.S. investigators.[16,17] Thus, the difference observed cannot be explained simply by differences in admission practices in the two places. Alternatively, the higher population density and levels of air pollution in Hong Kong may contribute to the higher rates of hospitalization. Further community-based and school-based studies may clarify whether the attack rates of influenza are higher in crowded communities like Hong Kong, thus accounting for the excess rates of hospitalization. However, one important factor is likely to be the clearer separation of influenza activity and RSV activity in Hong Kong in 1998 and 1999, allowing a closer approximation of the true burden of influenza.

The contribution of respiratory viruses other than RSV to hospitalization during base-line periods or periods in which influenza predominated could also be a source of confounding.[14,15] In our study, the contribution of parainfluenza and adenoviruses during base-line and peak influenza periods was similar. Moreover, their contribution was of a much smaller magnitude than that of influenza during periods in which influenza predominated. We are therefore confident that these viruses did not significantly confound our findings. In our study, children with acute respiratory disease associated with influenza had very low mortality rates, and there was no discernible influenza-related excess risk of death.

Ours is one of the few population-based studies to provide data on the effect of influenza on the rates of hospitalization of children in the tropics or subtropics and demonstrates that the disease burden may be even greater than that documented in temperate re-

gions.[10,11,17,18,25,26] Although our findings cannot be generalized to regions with different socioeconomic conditions, they provide data from an area outside the temperate region. They also highlight the value and limitations of data derived from an excess-hospitalization model.

Our findings contribute to the ongoing discussion of the cost–benefit ratio for universal vaccination of children.[17,18,27-32] The use of influenza vaccine is very limited in Hong Kong. Its use has been recommended since 1997 for elderly patients in institutions and since November 2000 for children with chronic lung disease (excluding asthma) or congenital heart disease or children who are receiving long-term aspirin therapy.[19] The lack of local or regional data on the burden of influenza and the uncertainty of the applicability of data from temperate regions have been major obstacles to developing a rational policy regarding wider vaccine use.

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REFERENCES

1. Shortridge KF, Stuart-Harris CH. An influenza epicentre? Lancet 1982;2:812-3.
2. Shortridge KF. The next pandemic influenza virus? Lancet 1995;346:1210-2.
3. Yuen KY, Chan PKS, Peiris M, et al. Clinical features and rapid viral diagnosis of human disease associated with avian influenza A H5N1 virus. Lancet 1998;351:467-71.
4. Isolation of avian influenza A(H5N1) viruses from humans — Hong Kong, May–December 1997. MMWR Morb Mortal Wkly Rep 1997;46:1204-7.
5. Fitzner KA, Shortridge KF, McGhee SM, Hedley AJ. Cost-effectiveness study on influenza prevention in Hong Kong. Health Policy 2001;56:215-34.
6. Hong Kong Government. Hong Kong coroners report. Hong Kong, China: Hong Kong Government Printer, 1993.
7. Fitzner KA, McGhee SM, Hedley AJ, Shortridge KF. Influenza surveillance in Hong Kong: results of a trial Physician Sentinel Programme. Hong Kong Med J 1999;5:87-94.
8. Adoption of global agenda on influenza. Wkly Epidemiol Rec 2002;77:191-5.
9. Adams PF, Marano MA. Current estimates from the National Health Interview Survey, 1994. Vital and health statistics. Series 10. No. 193. Hyattsville, Md.: National Center for Health Statistics, December 1995. (DHHS publication no. (PHS) 96-1521.)
10. Glezen WP, Taber LH, Frank AL, Gruber WC, Piedra PA. Influenza virus infections in infants. Pediatr Infect Dis J 1997;16:1065-8.
11. Prevention and control of influenza: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Morb Mortal Wkly Rep 2001;50(RR-4):1-44.
12. Drinka PJ, Gravenstein S, Krause P, et al. Non-influenza respiratory viruses may overlap and obscure influenza activity. J Am Geriatr Soc 1999;47:1087-93. [Erratum, J Am Geriatr Soc 1999;47:1363.]
13. Mullooly JP, Barker WH. Impact of type A influenza on children: a retrospective study. Am J Public Health 1982;72:1008-16.
14. Influenza and hospitalizations in children. N Engl J Med 2000;342:1752-3.
15. Glezen GP. Influenza control — unfinished business. JAMA 1999;281:944-5.
16. Izurieta HS, Thompson WW, Kramarz P, et al. Influenza and the rates of hospitalization for respiratory disease among infants and young children. N Engl J Med 2000;342:232-9.
17. Neuzil KM, Mellen BG, Wright PF, Mitchel EF Jr, Griffin MR. The effect of influenza on hospitalizations, outpatient visits, and courses of antibiotics in children. N Engl J Med 2000;342:225-31.
18. McIntosh K, Lieu T. Is it time to give influenza vaccine to healthy infants? N Engl J Med 2000;342:275-6.
19. Influenza Surveillance. Government of Hong Kong Special Administrative Region Department of Health. (Accessed November 5, 2002, at http://www.info.gov.hk/dh/diseases/.)
20. Woo PCY, Chiu SS, Seto WH, Peiris M. Cost-effectiveness of rapid diagnosis of viral respiratory tract infections in pediatric patients. J Clin Microbiol 1997;35:1579-81.
21. Chiu SS, Tse CYC, Lau YL, Peiris M. Influenza A infection is an important cause of febrile seizures. Pediatrics 2001;108:993. abstract. (Also available at http://www.pediatrics.org/cgi/content/full/108/4/e63.)
22. Neuzil KM, Wright PF, Mitchel EF Jr, Griffin MR. The burden of influenza illness in children with asthma and other chronic medical conditions. J Pediatr 2000;137:856-64.
23. Glezen WP, Decker M, Perrotta DM. Survey of underlying conditions of persons hospitalized with acute respiratory disease during influenza epidemics in Houston, 1978-1981. Am Rev Respir Dis 1987;136:550-5.
24. Simonsen L, Clarke MJ, Williamson GD, Stroup DF, Arden NH, Schonberger LB. The impact of influenza epidemics on mortality: introducing a severity index. Am J Public Health 1997;87:1944-50.
25. Szucs TD. Influenza: the role of burden-of-illness research. Pharmacoeconomics 1999;16:Suppl 1:27-32.
26. Sugaya N, Nerome K, Ishida M, et al. Impact of influenza virus infection as a cause of pediatric hospitalization. J Infect Dis 1992;165:373-5.
27. Kim HW, Brandt CD, Arrobio JO, Murphy B, Chanock RM, Parrott RH. Influenza A and B virus infection in infants and young children during the years 1957-1976. Am J Epidemiol 1979;109:464-79.
28. Cohen GM, Nettleman MD. Economic impact of influenza vaccination in preschool children. Pediatrics 2000;106:973-6.
29. Poland GA, Hall CB. Influenza immunization of schoolchildren: can we interrupt community epidemics? Pediatrics 1999;103:1280-2.
30. Monto AS. Prospects for pandemic influenza control with currently available vaccines and antivirals. J Infect Dis 1997;176:Suppl 1:S32-S37.
31. Edwards KM, Poehling KA. Influenza virus continues to pose new challenges. Pediatrics 2001;108:1004-5.
32. Neuzil KM, Griffin MR, Schaffner W. Influenza vaccine: issues and opportunities. Infect Dis Clin North Am 2001;15:123-41.