

# Influenza A Infection Is an Important Cause of Febrile Seizures

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**ABSTRACT.** *Objectives.* To compare the incidence of febrile seizures in children hospitalized for influenza A infection with parainfluenza and adenovirus infection and to examine the hypothesis that children hospitalized for influenza A (variant Sydney/H3N2) during the 1998 season in Hong Kong had more frequent and refractory seizures when compared with other respiratory viruses, including the A/Wuhan H3N2 variant that was present in the previous year.

*Methods.* Medical records of children between 6 months and 5 years of age admitted for influenza A infection in 1998 were reviewed. For comparison, records of children of the same age group with influenza A infection in 1997, and with parainfluenza and adenovirus infections between 1996 and 1998 were reviewed. Children who were afebrile or who had an underlying neurologic disorder were excluded.

*Results.* Of children hospitalized for influenza A in 1998 and 1997, 54/272 (19.9%) and 27/144 (18.8%) had febrile seizures, respectively. The overall incidence of febrile seizures associated with influenza A (19.5%) was higher than that in children hospitalized for parainfluenza (18/148; 12.2%) and adenovirus (18/199; 9%) infection, respectively. In children who had febrile seizures, repeated seizures were more commonly associated with influenza A infection than with parainfluenza or adenovirus infection (23/81 [28%] vs 3/36 [8.3%], odds ratio [OR] 4.3, 95% confidence interval: 1.2 to 15.4). Alternatively, children with influenza A infection had a higher incidence (23/416, 5.5%) of multiple seizures during the same illness than those with adenovirus or parainfluenza infection (3/347, 0.86%; OR 6.7, 95% confidence interval: 2.0–22.5.) The increased incidence of febrile seizures associated with influenza A was not attributable to differences in age, gender, or family history of febrile seizure. Multivariate analysis, adjusted for peak temperature and duration of fever, showed that hospitalized children infected with infection A had a higher risk of febrile seizures than those who were infected with parainfluenza or adenovirus (OR 1.97).

Influenza A infection was a significant cause of febrile seizure admissions. Of 250 and 249 children admitted to Queen Mary Hospital for febrile seizures in 1997 and 1998, respectively, influenza A infection accounted for 27 (10.8%) admissions in 1997 and 54 (21.7%) in 1998. During months of peak influenza activity, it accounted for up to 35% to 44% of febrile seizure admissions. In contrast, parainfluenza, adenovirus, respiratory syncytial virus,

and influenza B had a smaller contribution to hospitalizations for febrile seizures, together accounting for only 25/250 (10%) admissions in 1997 and 16/249 (6.4%) in 1998.

*Conclusion.* The influenza A Sydney variant (H3N2) was not associated with an increased risk of febrile seizures when compared with the previous influenza A Wuhan variant (H3N2) or H1N1 viruses. However, in hospitalized children, influenza A is associated with a higher incidence of febrile seizures and of repeated seizures in the same febrile episode than are adenovirus or parainfluenza infections. The pathogenesis of these observations warrants additional studies. Complex febrile seizures, particularly multiple febrile seizures at the time of presentation, have been thought to carry an adverse long-term prognosis because of its association with a higher incidence of epilepsy. Repeated febrile seizures alone, particularly if associated with influenza A infection, may not be as worrisome as children with complex febrile seizures because of other causes, which requires additional investigation. This may subsequently have an impact on reducing the burden of evaluation in a subset of children with complex febrile seizures. *Pediatrics* 2001;108(4). URL: <http://www.pediatrics.org/cgi/content/full/108/4/e63>; influenza A, febrile seizures, febrile convulsions, multiple seizures, adenovirus, parainfluenza.

ABBREVIATIONS. SD, standard deviation; OR, odds ratio.

Febrile seizures are defined as an event in infancy or childhood, usually occurring between 6 months and 5 years of age, associated with fever but without evidence of intracranial infection or other definable cause. Seizures with fever in children who have suffered a previous afebrile seizure are excluded.<sup>1</sup> Of children of North American or European background, 2% to 5% will experience 1 or more febrile convulsion before the age of 5, whereas in Japan 6% to 9% of infants and children experience febrile seizures.<sup>2,3</sup> However, the overall incidence of febrile seizure in febrile children is not known. The risk of febrile seizure is associated with many factors, including family history.<sup>4</sup> The exact pattern of inheritance is uncertain, but many authors favor a multifactorial model.<sup>5,6</sup> Recent studies have identified gene loci associated with febrile seizures on chromosomes 5, 8, and 19.<sup>7–10</sup> Febrile seizures are also strongly age-dependent with the median age of first presentation between 17 and 23 months. Febrile seizures occur more frequently in boys than in girls.

Viral infections have been implicated as a cause of febrile seizures. In a study of 73 children admitted with febrile convulsion, a viral cause could be implicated for 86% of the children.<sup>11</sup> Despite the apparent

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importance of viral illness in precipitating febrile seizures, the contribution of influenza A has not been fully elucidated. Data on the association of influenza A infection and febrile seizures in the English-language literature is limited, and there is a wide discrepancy in the reported incidence. Some reports have included children with underlying causes for seizures, and their relevance to the pathogenesis of febrile seizures is limited.<sup>12-15</sup>

In 1998, a new influenza A antigenic variant, the H3N2 Sydney virus, appeared in Hong Kong. Some pediatricians had the impression that febrile seizures associated with this new variant were more common than previously seen with influenza A. In 1998, 98.7% of influenza A viruses isolated in Hong Kong were H3N2 (Sydney variant) with 1.3% H1N1, whereas in 1997, the influenza A isolates were 89.4% H3N2 (Wuhan variant), 8% H1N1, and 2.6% H5N1. A retrospective cohort study was conducted to examine the hypotheses that influenza A (Sydney variant/H3N2) caused more frequent and more refractory febrile seizures than other respiratory viruses, including influenza A (Wuhan variant/H3N2 and H1N1).

## METHODS

### Study Populations

A retrospective chart review was conducted on all children between 6 months and 5 years of age who were admitted with influenza A infection in 1998 to Queen Mary Hospital. This university-affiliated teaching hospital has 120 pediatric beds serving a pediatric population of about 100 000 (under 15 years of age) on Hong Kong Island. Nonpediatricians staff the emergency department at Queen Mary Hospital, and all children who present with febrile seizures are routinely admitted. For comparison, charts of children of the same age admitted for influenza A in 1997, and with parainfluenza and adenovirus infections between 1996 and 1998 were reviewed. Parainfluenza and adenovirus were chosen because they also cause an acute febrile illness in young children. Three years' data were reviewed for parainfluenza and adenovirus because of the smaller number of children hospitalized each year with these 2 viral infections. Children who were afebrile or had an underlying seizure disorder were excluded. Children with H5N1 infection were also excluded. The list of all the children admitted for febrile seizures in 1997 and 1998 were also retrieved.

### Definitions

Febrile seizure was defined as a seizure event occurring between 6 months and 5 years of age associated with fever but without evidence of intracranial infection or other definable cause. Seizure was defined as an involuntary generalized tonic, clonic, or tonic-clonic movement associated with impaired consciousness. The maximum temperature was the rectal temperature recorded during the course of hospitalization. The temperature closest to the time of seizure was that recorded either closest to the time of seizure at home or at the emergency department. If >1 episode of febrile seizures occurred, the temperature closest to the first episode was used.

### Laboratory Methods

Throughout the year, all children who were admitted with fever and upper as well as lower respiratory symptoms routinely had their nasopharyngeal aspirate sent for rapid viral antigen detection and culture, irrespective of the absence or presence of seizure. At the discretion of the attending pediatrician, some children with symptoms consistent of a viral infection also had their nasopharyngeal aspirate specimens tested in the absence of fever. The antigen detection test detected a panel of respiratory viruses that included influenza A; parainfluenza types I, II, and III; adenovirus; and respiratory syncytial viruses using immunofluorescence techniques. These results were usually available within 24 hours of admission.

## Statistical Analysis

Comparisons of age, maximum temperature, and duration of fever among the 4 groups of children as well as the subgroups with and without febrile seizures were performed using 1-way analysis of variance with a posthoc Tukey-Kramer test. A  $\chi^2$  test was used to compare the sex ratio among these groups. An unpaired *t* test was used to compare the mean of the age, maximum temperature, and the duration of fever between the groups with and without febrile seizures. The Fisher exact test with Yates continuity correction was used to compare the incidence of multiple seizures among children with influenza infection with children with adenovirus and parainfluenza infections. Multivariate logistic-regression analysis was used to examine the risk of febrile seizures after adjustment for individual risk factors.

## RESULTS

### Demographic and Clinical Features of Children Hospitalized for Influenza, Parainfluenza, and Adenovirus Infections

Two hundred eighty children and 150 children between 6 months and 5 years of age were admitted with influenza A infection in 1998 and 1997, respectively. One hundred seventy-two children and 220 children were admitted for parainfluenza and adenovirus infection, respectively. Thirty-three children without fever were excluded: 4 with influenza A in 1997, 6 with influenza A in 1998, 17 with parainfluenza, and 6 with adenovirus. Twenty-five children with underlying seizure disorders were also excluded: 2 with influenza A in 1997, 2 with influenza A in 1998, 7 with parainfluenza, and 14 with adenovirus. One child with adenovirus had no febrile seizures but seemed drowsy with decreased responsiveness on admission and was diagnosed as encephalopathy by electroencephalogram and was also excluded from the study. Two hundred seventy-two and 144 children admitted with influenza A infection in 1998 and 1997 satisfied the recruitment criteria, as did 148 children with parainfluenza and 199 children with adenovirus infection. The characteristics of these 4 groups were compared (Table 1). Children with parainfluenzae infection were significantly younger and those with adenovirus infection were significantly older than the influenza A-infected children. All 4 groups of children had a high peak temperature but children with parainfluenza infection had a lower maximum temperature. Duration of fever was shorter in the groups of children infected with parainfluenza and influenza A in 1997. There was no difference in the male-to-female ratio.

### Incidence of Febrile Seizures in Children Hospitalized With Influenza, Parainfluenza, and Adenovirus Infections

There was no difference in the incidence of febrile seizures in children admitted for influenza in 1997 (27/144; 18.8%) and 1998 (54/272; 19.9%; *P* = .9). There was also no difference in the incidence of febrile seizures between children with parainfluenza (18/148, 12.2%) and adenovirus (18/199, 9%; *P* = .38). However, the overall incidence of febrile seizure associated with influenza A infection (81/416, 19.5%) in 1997 and 1998 was significantly higher than that with parainfluenza and adenovirus infections (36/347, 10.4%; *P* = .0004).

**TABLE 1.** Comparison of Age, Maximum Temperature, and Duration of Fever in Children Infected With Different Respiratory Viruses

|  | Mean  | SD   | P Value                         |                                 |                         |                            |
|--|-------|------|---------------------------------|---------------------------------|-------------------------|----------------------------|
|  |       |      | Influenza A (1997)<br>(n = 144) | Influenza A (1998)<br>(n = 272) | Adenovirus<br>(n = 199) | Parainfluenza<br>(n = 148) |
| Age (mo) <i>P</i> < .001                     |       |      |                                 |                                 |                         |                            |
| Influenza A (1997)                           | 24.92 | 14.7 | —                               | .2519                           | <.001                   | <.05                       |
| Influenza A (1998)                           | 27.69 | 14.5 | .2519                           | —                               | <.001                   | <.001                      |
| Adenovirus                                   | 33.17 | 15.3 | <.001                           | <.001                           | —                       | <.001                      |
| Parainfluenza                                | 21.12 | 12.4 | <.05                            | <.001                           | <.001                   | —                          |
| Maximum temperature (°C)<br><i>P</i> < .0001 |       |      |                                 |                                 |                         |                            |
| Influenza A (1997)                           | 39.6  | 0.58 | —                               | 1.0                             | .130                    | <.001                      |
| Influenza A (1998)                           | 39.6  | 0.63 | 1.0                             | —                               | .087                    | <.001                      |
| Adenovirus                                   | 39.7  | 0.62 | .130                            | .087                            | —                       | <.001                      |
| Parainfluenza                                | 39.2  | 0.67 | <.001                           | <.001                           | <.001                   | —                          |
| Duration of fever (d)<br><i>P</i> < .0001    |       |      |                                 |                                 |                         |                            |
| Influenza A (1997)                           | 3.75  | 1.93 | —                               | .054                            | <.001                   | .218                       |
| Influenza A (1998)                           | 4.40  | 2.11 | .054                            | —                               | .056                    | <.001                      |
| Adenovirus                                   | 4.78  | 2.21 | <.001                           | .056                            | —                       | <.001                      |
| Parainfluenza                                | 3.51  | 2.49 | .218                            | <.001                           | <.001                   | —                          |

The current episode of febrile seizures represented the first episode in a significant percentage of the children, regardless of the infectious organism—18/27 (66.7%) in those with influenza A infection in 1997, 33/54 (61.1%) in children with influenza A infection in 1998, 13/18 (72.2%) in those with parainfluenza infection, and 8/18 (44.4%) in those with adenovirus infection (*P* = .33). Likewise, there was no statistically significant difference in the incidence of a positive family history of febrile seizures in these children—6/27 (22%) in the children with influenza A in 1997, 13/54 (24%) in children with influenza A in 1998, 4/18 (22.2%) in those with parainfluenza, and 6/18 (33.3%) with adenovirus infection (*P* = .8).

All initial episodes of febrile seizure happened at home. All reported seizures were of generalized tonic-clonic in nature except for a child with influenza in 1998 who had an atonic seizure. Only 8 children had their febrile seizures after 24 hours of fever onset: 3 each with influenza A infection in 1997 and 1998, and 2 with adenovirus.

#### Characteristics of Children With and Without Febrile Seizures Hospitalized With Influenza, Parainfluenza, and Adenoviruses

Children with or without febrile seizures with each viral infection were compared and found to have no difference in age and gender (data not shown). Children infected with influenza A in 1998 with febrile seizures had a mean maximum temperature of 39.8°C (standard deviation [SD]: 0.52) whereas those without febrile seizures had a mean maximum temperature of 39.6°C (SD: 0.63; *P* = .03). However, when the mean maximum temperature of children with influenza A in 1998 who had no febrile seizures was compared with the temperature recorded closest to the time of seizure in the febrile seizures group, the mean temperature was significantly higher in the group without febrile seizures: 39.6°C (SD: 0.63) vs 39.3°C (SD: 0.69; *P* = .008). There were no differences in maximum temperature be-

tween the seizure and nonseizure patients for any of the other virus groups. Children with adenovirus infection who had no febrile seizures had more prolonged fever than those who had febrile seizures (4.78 ± 2.2 days vs 3.4 ± 0.9 days; *P* = .0001). No difference was seen with any of the other virus groups.

In univariate analysis, significant factors for risk of febrile seizures include influenza infection (*P* = .001), a high peak temperature (*P* = .019), and a shorter duration of fever (*P* = .0042). Age was not a significant factor. The shorter duration of fever associated with an increased risk of febrile seizure was attributable to the skewing from children infected with adenovirus having a significantly longer duration of fever, and few of these children had febrile seizures. Multivariate analysis, adjusted for peak temperature and duration of fever, showed that hospitalized children infected with influenza A had a higher risk of febrile seizures than those who were infected with parainfluenza or adenovirus. (*P* = .0005; odds ratio [OR] 1.97).

#### Characteristics and Clinical Manifestations of Febrile Seizures of Children Hospitalized With Influenza, Parainfluenza, and Adenoviruses

Children who had febrile seizure associated with parainfluenza were significantly younger than those infected with adenovirus (Table 2). Children who had febrile seizures and parainfluenza had lower peak temperatures and a shorter fever duration than those who were infected with influenza or adenovirus.

Some children infected with adenovirus or influenza had >1 episode of febrile seizure during the same acute illness, but no child with parainfluenza infection did so. All episodes of repeated seizures were witnessed by experienced nursing and medical personnel in the hospital and were generalized tonic-clonic in nature. Infection with influenza A in both 1997 and 1998 was associated with a high incidence

**TABLE 2.** Comparison of Age, Maximum Temperature, and Duration of Fever in Children With Febrile Seizure Infected With Different Respiratory Viruses

|  | Mean  | SD    | P Value                        |                                |                        |                           |
|--|-------|-------|--------------------------------|--------------------------------|------------------------|---------------------------|
|  |       |       | Influenza A (1997)<br>(n = 27) | Influenza A (1998)<br>(n = 54) | Adenovirus<br>(n = 18) | Parainfluenza<br>(n = 19) |
| Age (mo) <i>P</i> < .005                     |       |       |                                |                                |                        |                           |
| Influenza A (1997)                           | 27.00 | 11.76 | —                              | .616                           | <.05                   | .803                      |
| Influenza A (1998)                           | 28.24 | 9.77  | .616                           | —                              | <.05                   | .446                      |
| Adenovirus                                   | 35.11 | 11.82 | <.05                           | <.05                           | —                      | <.05                      |
| Parainfluenza                                | 26.11 | 11.50 | .803                           | .446                           | <.05                   | —                         |
| Maximum temperature (°C)<br><i>P</i> < .0001 |       |       |                                |                                |                        |                           |
| Influenza A (1997)                           | 39.8  | 0.56  | —                              | .874                           | .909                   | <.05                      |
| Influenza A (1998)                           | 39.8  | 0.52  | .874                           | —                              | 1.0                    | <.01                      |
| Adenovirus                                   | 39.8  | 0.59  | .909                           | 1.0                            | —                      | <.05                      |
| Parainfluenza                                | 39.1  | 0.54  | <.05                           | <.01                           | <.05                   | —                         |
| Duration of fever (d)<br><i>P</i> < .05      |       |       |                                |                                |                        |                           |
| Influenza A (1997)                           | 3.70  | 1.73  | —                              | .238                           | .490                   | <.05                      |
| Influenza A (1998)                           | 4.46  | 2.58  | .238                           | —                              | .097                   | <.05                      |
| Adenovirus                                   | 4.88  | 2.00  | .490                           | .097                           | —                      | <.05                      |
| Parainfluenza                                | 3.49  | 2.52  | <.05                           | <.05                           | <.05                   | —                         |

of having repeated seizures during the same illness (6/27 [22.2%] and 17/54 [31.5%], respectively, *P* = .44). Three (16.6%) of the 18 children with seizures associated with adenovirus had repeated seizures. Repeated seizures in children who had febrile seizures associated with influenza A infection were significantly more common than in children who had febrile seizures associated with parainfluenza or adenovirus infection (23/81 [28%] vs 3/36 [8.3%], *P* = .02; OR 4.3, 95% confidence interval: 1.2 to 15.4). When all children with influenza A infection are compared with children with adenovirus and parainfluenza infection, the difference in incidence of repeated seizures is even more remarkable: 23/416 (5.5%) versus 3/347 (0.86%), *P* = .0004, OR 6.7, 95% confidence interval: 2.0 to 22.5. Of the children infected with influenza A who had repeated febrile seizures, 12 children had 2 seizures, 2 children had 3 episodes, 2 children had 5 repeated seizures, and 1 child presented with status epilepticus. All children with repeated episodes of seizure had their seizures while febrile and were neurologically asymptomatic between episodes. Some of these episodes occurred within the same day whereas others were separated by a day. Only 6 brain computed tomography and 6 lumbar punctures were performed on the 83 children with febrile seizure associated with influenza A infection, and the results were all normal. Polymerase chain reaction assay for influenza was not performed on the cerebrospinal fluid. A total of 17 electroencephalograms were performed. Except for the child with status epilepticus, all were normal or showed postictal changes.

#### Viral Cause of All Children Admitted With Febrile Seizures

Two hundred fifty children and 249 children were admitted to Queen Mary Hospital for febrile seizures in 1997 and 1998, respectively. Of these hospitalizations, influenza A infection accounted for 27/250

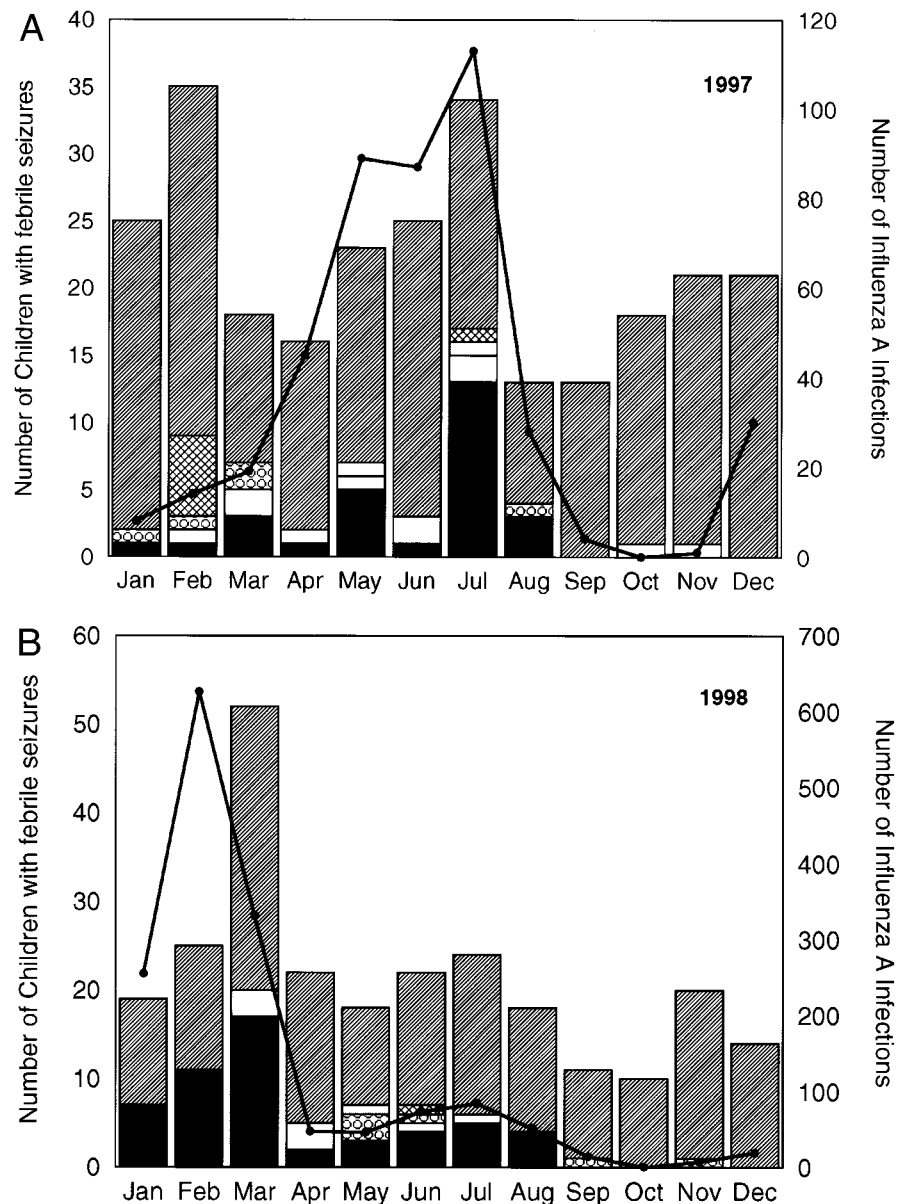
(10.8%) in 1997 and 54/249 (21.7%) in 1998, and accounted for up to 35% to 44% of febrile seizures admissions in the months during peak influenza activity (Fig 1A and B). Parainfluenza, adenovirus, respiratory syncytial virus, and influenza B had a minimal contribution to hospitalizations for febrile seizures, together accounting for 25/250 (10%) in 1997 and 16/249 (6.4%) in 1998.

#### DISCUSSION

In children ill enough to be hospitalized, influenza A was associated with a higher incidence of febrile seizures and of repeated seizures in the same febrile episode than adenovirus or parainfluenza infections. The influenza A Sydney variant (H3N2) was not associated with an increased risk of febrile seizures when compared with the previous influenza A Wuhan variant (H3N2) or H1N1 viruses. The clinical impression of such an association was probably because of the increased number of influenza admissions associated with the emergence of the antigenic variant "Sydney-like" H3N2 virus in 1998. Influenza A also caused more instances of repeated seizures within the same acute illness, an uncommon feature for febrile seizure in general. Adjusted multivariate analysis indicated that influenza A infection was an independent risk for febrile seizures. The clinical impact and the health benefits of influenza immunization for healthy children have recently been a focus of debate. Excess rates of hospitalization for cardiopulmonary diseases of previously healthy children during influenza A seasons has been reported.<sup>16,17</sup> We now document that influenza A also additionally contributes to hospitalization through triggering febrile seizures.

Despite increasing reports on influenza A-associated encephalitis or encephalopathy, there is not much information on seizures associated with influenza A infection.<sup>18,19</sup> The incidence of convulsion associated with influenza A infection had been re-

**Fig 1.** Admission because of febrile seizures in relation to infections caused by influenza A and other respiratory viruses in (A) 1997 and (B) 1998. The viruses denoted are ■, influenza A; ▨, influenza B; □, adenovirus; ▩, parainfluenza; ▧, RSV; and negative nasopharyngeal aspirate. The number of all influenza A diagnoses made in the Queen Mary Hospital laboratory (—●—) on a monthly basis is provided to illustrate the seasonality of the influenza A infection. The microbiology laboratory at Queen Mary Hospital is the Hospital Authority reference laboratory for Hong Kong Island, and the number includes specimens from the whole region.



ported to range from 6% to 40%.<sup>12-15</sup> The large variation in the incidence of febrile seizure associated with influenza A seen in different studies can be partially explained by differences in age.<sup>15</sup> In other studies, the patient population was heavily skewed in favor of those with severe complications, including convulsions. Thirty-one of 61 children admitted during an epidemic in Newcastle on Tyne were admitted because of convulsion.<sup>12</sup> Most studies were also limited by the small number of patients included. The present study represents the largest report of children with febrile seizures associated with influenza A infection in hospitalized children. Our hospital is a university teaching hospital that provides primary as well as tertiary care to a population of 100 000 <15 years of age. The emergency department is heavily used by parents of children with acute febrile illnesses as an alternative to private physician consultation, especially after office hours

or if the children are still febrile after a physician visit in the community. In addition, physicians who are not pediatricians staff our emergency department and they have a low threshold for admitting young children with acute illnesses. This prevented excessive skewing of our study sample through only admitting children with more severe illness or those with febrile seizures. The number of afebrile children hospitalized with various viral infections and excluded from this study attests to this point. The availability of rapid diagnosis for a range of respiratory viruses and the documentation that such investigation is cost-effective leading to shorter hospital stay and reduced antibiotic use has resulted in the almost universal use of viral investigation of children with febrile illnesses admitted to our hospital.<sup>20</sup> Thus, there is little likelihood of bias in diagnosis because of selective viral investigation of more seriously ill children.

The impact of influenza on febrile seizures is also reflected by the correlation between the seasonality of influenza A infections and that of febrile seizures overall (Fig 1). Although a significant number of febrile seizures have no respiratory viral diagnosis, there is a clear increase of febrile seizures associated with the influenza A season, both in 1997 and 1998. Much of the seasonal changes in febrile seizures are attributable to influenza A. It is noteworthy that the seasonality of influenza A in Hong Kong, and the tropics in general, is markedly different to that in temperate regions. In Hong Kong, influenza A activity peaks in February or March, but there may be a second summer peak of virus activity as was seen in 1997.

There have been no previous reports of an association between influenza A and repeated febrile seizures during the same febrile illness. Population-based studies have shown complex febrile seizures to comprise approximately 20% of all febrile seizures. Febrile seizures are characterized as complex if they are focal, multiple, or prolonged. Thus, the incidence of repeated seizures alone should be much <20%. The percentage of patients with febrile seizures associated with influenza A infection who developed repeated seizures (28%) was therefore significantly higher than expected. Because these children had isolated episodes of seizure that fit the description of febrile seizure with a very short postictal drowsy period and were perfectly alert and well between seizures, these were repeated episodes of seizures and not manifestations of encephalopathy or encephalitis. Classical descriptions of febrile seizures distinguished complex febrile seizures from simple febrile seizures because previous studies have shown complex febrile seizures, particularly multiple febrile seizures at the time of presentation, were associated with a higher incidence of subsequent epilepsy.<sup>21-23</sup> The findings from this study may stimulate rethinking of the prognostic implications of complex febrile seizures and may have an impact on reducing the burden of evaluation in a subset of children with complex febrile seizures. Repeated febrile seizures alone, particularly if associated with influenza A infection, may not be as worrisome as children with other features of complex febrile seizures. Definitive longitudinal studies of long-term outcome are needed for these children with influenza A infection.

There has been much discussion in the literature on whether the height of the temperature or the rate of its rise is more important in the precipitation of a seizure, but the majority of data point to the importance of the height of temperature in eliciting febrile seizures.<sup>24,25</sup> The exact body temperature at the time of the seizure is known in only a minority of patients. The difference in the incidence of febrile seizure in our children cannot be solely explained by a difference in the height of fever. Even if the fever itself is regarded as an important and always previous event, the paradox remains that at least 65% and as many as 82% of children who have febrile seizures have had previous febrile illnesses uncomplicated by seizures. There is a possibility that the underlying infection that causes the fever may contribute to triggering the

event. Some viruses, such as human herpesvirus 6, have been shown to have neurotropic properties.<sup>26</sup> Recent studies have indicated that influenza may, on occasion, infect the central nervous system and lead to encephalopathy/encephalitis. There is a recent report of a novel amino acid substitution at the receptor-binding site on the hemagglutinin genes of influenza A that may correlate with viral tropism for the brain.<sup>27</sup> Influenza A, with or without amino acid substitution at the receptor-binding site of the hemagglutinin-1 domain, may be more neurotropic than the other respiratory viruses. This may explain why for the same height of fever and equivalent risk factors, children with influenza A infection tend to have more seizures and more repeated seizures. Additional studies investigating such a hypothesis are warranted.

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