The September epidemic of asthma hospitalization: School children as disease vectors

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Asthma diagnosis and treatment

Background: Viral infections are associated with the majority of asthma exacerbations in children and adults. Increased asthma hospitalization rates of children and adults, particularly in the early fall, have been observed to follow school vacations.

Objective: We sought to determine the sequence of timing of September asthma hospitalization epidemics in children and adults and to determine whether school-age children are the primary source of transmission of agents that cause them.

Methods: By using Canadian asthma hospital admission data from 1990 to 2002, we examined geographic variation in the timing of fall asthma epidemics and applied mathematical modeling to estimate their exact timing and magnitude in school-age children, preschool children, and adults, and relation to school return.

Results: The September asthma hospitalization epidemic peak occurred in school-age children each year on average 17.7 (95% CI, 16.8-18.5) days after Labor Day. Similar epidemics of lesser magnitude were observed in preschool children peaking 1.7 (95% CI, 0.9-2.5; $P < .001$) days later, and in adults 6.3 (95% CI, 4.7-7.9; $P < .001$) days later than in school-age children. The epidemics peaked 4.2 (95% CI, 1.2-7.1; $P < .001$) days earlier in school-age children in northernmost compared with southernmost latitudes.

Conclusion: September epidemics of asthma hospitalizations in Canada have a precise relationship to school return after the summer vacation. It may be speculated that school-age children transmit the agents responsible for the epidemic to adults. Measures to improve asthma control and reduce transmission of infections should be directed at children with asthma before school return. (J Allergy Clin Immunol 2006;117:557-62.)

Key words: *Asthma exacerbations, school return, rhinovirus, hospitalization, transmission of infection, asthma control*

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Epidemics of exacerbations of asthma requiring hospitalization of children in late summer and early fall have been reported to occur in many Northern Hemisphere countries,[1-9] including Canada,[1,2] the United States,[3,4] the United Kingdom,[5] Mexico,[6] Israel,[7] Finland,[8] and Trinidad.[9] Asthma exacerbation epidemics have also been reported in the same period in adults.[2,5]

In Canada, the annual cycle of asthma exacerbations, which has been consistent in form for several years, reaches its peak in September and is most intense in children.[1] We had observed previously that the peak of this epidemic in children in 4 regions of Canada—the Atlantic Provinces, Ontario, the Prairie Provinces, and British Columbia—occurred most frequently in the third week of September.[10]

Viral respiratory tract infections, particularly of rhinoviruses, are associated with the majority of asthma exacerbations in both children[11,12] and adults.[13,14] Elevated rates of asthma hospitalization in children and adults and higher rates of respiratory viral infection in children have been reported to coincide,[15,16] with both greater during periods of school attendance,[16] and a close association of high rates of asthma exacerbation in children to school return after Labor Day has been demonstrated.[17]

Rhinovirus infections have been shown to be most common in early fall,[18] and school-age children have been shown to introduce rhinovirus infections into their families 3 times more frequently than working adults.[19] During the 3 weeks spanning the September asthma exacerbation peak period in 2001, in a major city in Ontario, more than 60% of all school-age children presenting to emergency departments with asthma had viral infections, predominantly of rhinovirus.[20]

In major cities across Canada, there is a significant relation of daily increases in the number of hospital admissions for asthma to aeroallergen levels, and high levels of these are common in the summer months and during the period of school return after Labor Day.[21]

The objective of this study was to compare the timing of the September asthma hospitalization epidemic between age groups and regions of different climate to determine

Abbreviations used
CIHI: Canadian Institute for Health Information
RTI: Respiratory tract infection

whether factors that children are exposed to after school return may be its primary cause.

METHODS

Hypotheses

In Canada, the great majority of school-age children return to school after 2 to 3 months vacation on the first Tuesday in September immediately after Labor Day Monday. We hypothesized the following:

If the September epidemic of asthma was *primarily* precipitated by increased exposure to transmissible agents after school return rather than aeroallergens, its peak would track the timing of Labor Day.

If school-age children are vectors of transmission of agents causing asthma exacerbations, we would observe delays between asthma hospitalization peaks in them, those in adults, and possibly those in pre-school age children, and that these secondary peaks would be of lesser magnitude.

Residents of northern areas of Canada experience colder temperatures earlier than southern residents. We hypothesized that these areas would have earlier exposure to factors, including some viral infections, associated with colder weather and earlier epidemic peaks of asthma hospitalization than those in the south.

Source data

In Canada, abstracts of all inpatient hospitalization episodes, with the exception of those for Quebec, are forwarded to the Canadian Institute for Health Information (CIHI).

Data for all 256,843 hospitalizations with a principal diagnosis of asthma (International Classification of Diseases, Ninth Edition [ICD-9], 493.0-493.9) that occurred in Canada, excluding Quebec, between April 1990 and March 2003 for patients age 2 to 49 years were obtained from CIHI, providing data for 13 September peak periods. In 1990, a unique patient identification number was added to each record. March 2003 was the latest month for which data were available. Because cycles of asthma hospitalization in patients having 1 or multiple admissions did not differ (data not shown), all admissions were counted as single events. Data were assigned to ranges of latitude of residence by using standard postal code conversion files (Mapinfo Canada Inc, Toronto, Canada). Because more stringent privacy requirements, restricting access to geographic location of patient residence, were implemented in 2001, analyses of differences between latitude of residence were confined to the September epidemic periods from 1990 to 2000.

Although no specific validation study for the assignment of diagnoses of asthma in children has been performed for Canadian hospitalization data, reabstraction studies over all age groups have examined ambulatory care sensitive conditions, which include asthma, and found wrong assignment in 10.7% of records.[22] For pneumonias, the error rate was 6.9%. There is no evidence that wrong diagnostic assignment varies geographically or by time of year, and we concluded our analyses would not be biased by this. For comparison of annual cycles of hospitalization for respiratory tract infections (RTIs) and asthma, we obtained data for all 184,983 hospitalizations for RTI (ICD-9, 460-466.1, excluding 463 and 480-487.9) for patients age 2 to 49 years that occurred in Canada, excluding Quebec, between April 1995 and March 2003.

The Privacy, Confidentiality and Security Committee of CIHI approved acquisition and application of the data used in this study.

Definitions

From north to south, Canada was divided into 4 latitude ranges: above 52°, 51° and 52°, 44° to 50°, and below 44°. These ranges permitted at least 1 major population center to be included in each.

Age groups

Data were aggregated into 3 age groups: school-age children 5 to 15 years; preschool children age 2 to 4 years, considered to be less likely to attend full time school programs in Canada; and adults age 16 to 49 years.

Mathematical modeling of September epidemics

We used mathematical modeling to determine the precise timing of the peak of the epidemic for each year in each age group and latitude to permit analysis of the relationships between the timings of the epidemic peaks and school return. Examination of plots of the frequency of asthma hospitalization by week of the year showed that the early fall asthma epidemic peak period appeared as a unimodal peak over a curvilinear background. We tested the fit of a nonlinear least-squares model combining a normal distribution superimposed on a quadratic background to the data for weeks 30 to 42 of each year. Over the period of 13 years, the model explained between 98.0% and 99.4% of the variation in the data, and we therefore elected to retain it rather than formally evaluate other models. The equation for the model is $f(x)=a_0+a_1x+a_2x^2+a_3e^{\{-a_4(x-a_5)^2\}}$ in which $a_0 + a_1x + a_2x^2$ is the background, a_3 is the peak height above the background, a_4 is related to the variance of the normal distribution, and a_5 is the peak centroid. Calculation of the peaks' timings using the equation was performed using the Slide-Write computer program (Advanced Graphics Software, Encinitas, Calif).

Statistical analysis

Poisson regression was used to examine possible trends in the September epidemic of asthma over the study years. Computed peak timings and heights were entered into secondary databases to analyze differences between age groups and years using repeated-measures ANOVA, with 13 observations (years 1990-2002) and 3 age groups, Pearson correlation coefficient, or Student *t* test. Because numbers of events were too low to permit the analysis of characteristics of the peak in latitude ranges or individual years of age between study years, computed peak timings and heights for data aggregated across study years were used for these purposes.

RESULTS

Descriptive analysis of asthma hospitalization in Canada, 1990 to 2002

During the study period, there were 74,361 hospital admissions for asthma in subjects aged 2 to 4 years, 82,899 in subjects 5 to 15 years, and 99,583 in subjects 16 to 49 years. Although overall hospitalization rates for asthma were highest in the group 2 to 4 years old, the magnitude of the early fall peak in asthma hospitalization as a multiple of the weekly mean number of hospitalizations, shown in Fig 1, *A*, was greatest in the group 5 to 15 years old, followed by the group 2 to 4 years old and adults. Fig 1, *B*,

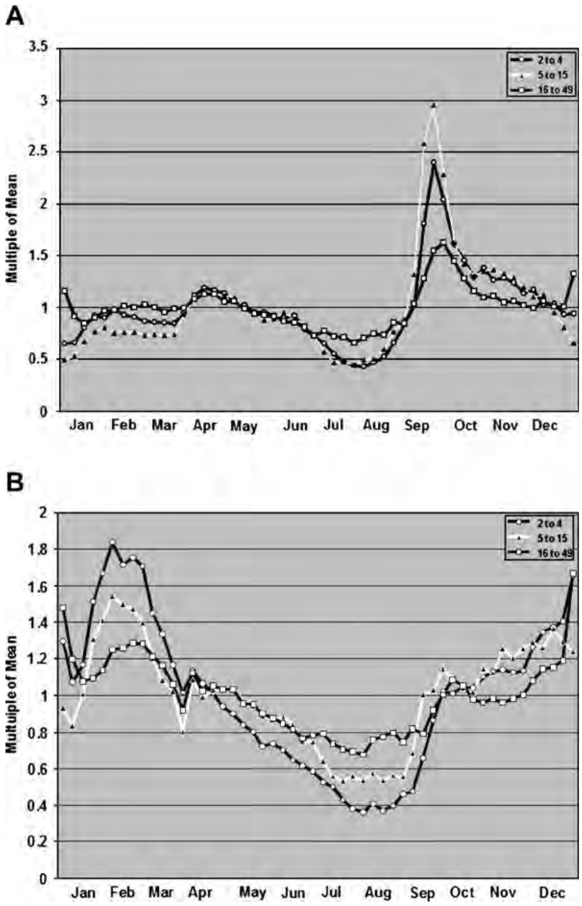

FIG 1. A, The annual cycle of asthma hospitalization by age group in Canada by week of the year. Data for all hospitalizations in Canada (excluding Québec) from April 1990 to March 2003 summarized over a single year. **B,** The annual cycle of hospitalization for respiratory tract infections by age group in Canada by week of the year. Data for all hospitalizations in Canada (excluding Québec) from April 1995 to March 2003 summarized over a single year.

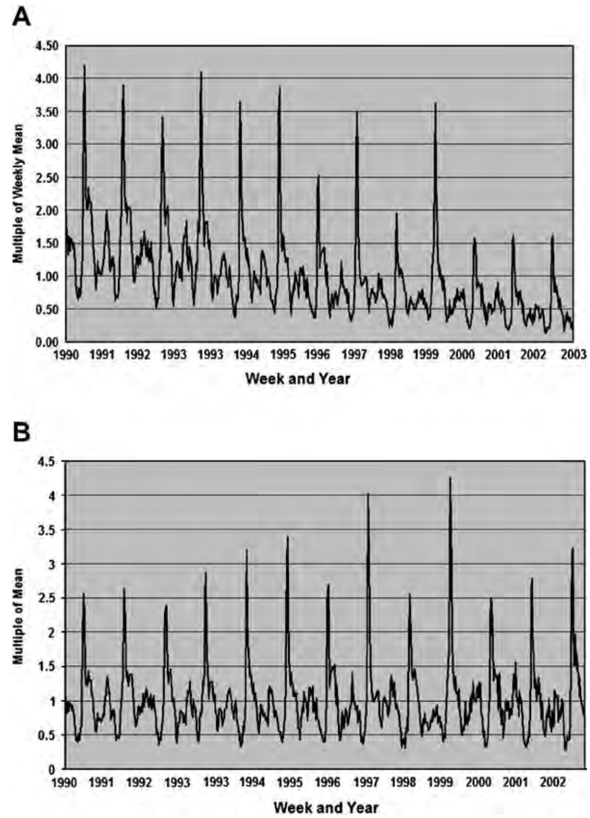

FIG 2. A, The cycle of asthma hospitalization of children age 5 to 15 years from April 1990 to March 2003 as multiples of the weekly mean number of hospitalizations over the whole period. **B,** The cycle of asthma hospitalization of children age 5 to 15 years from April 1990 to March 2003 as multiples of the weekly mean number of hospitalizations within each year.

shows the cycles of hospitalization for RTI, which are at their low point in summer, accelerating through fall to peaks that occur in the winter months. The cycles observed for asthma and RTI are distinct, suggesting that there is reasonable diagnostic discrimination between asthma and RTI in the hospitalization data.

Fig 2, *A,* shows the cycle of asthma hospitalization in school-age children from 1990 to 2002 as multiples of the overall weekly mean number of hospitalizations. The magnitude of the September peak appeared to decline, although this was not statistically significant (slope −.072; $P = .10$). This decline was common to all study age groups (data not shown). Fig 2, *B,* shows the cycle of asthma hospitalization over the study period in school-age children as multiples of the within-year weekly mean number of hospitalizations. The height of the September peak relative to within-year weekly hospitalization has remained quite stable (slope .016; $P = .71$), suggesting that the factors that cause the September epidemic have had a consistent effect within each year.

The September epidemic peak was found to occur during week 38 (September 17-23) in school-age and preschool children in every year except in 1992 (week 39) and 1997 (week 37), whereas the peak timing in adults occurred in week 38 in 3 years (1990, 1992, and 1993), week 39 in 6 (1991 and 1994-1998), and week 40 in 2 (1999 and 2000). The late peak in children in 1992 occurred when Labor Day was at its latest possible date and the early peak in 1997, when it was at its earliest.

Timing of the epidemic peaks relative to Labor Day using modeled data

Over the 13 study years, the average timing, derived from the model, of the epidemic peak in school-age children was 17.7 (95% CI, 16.8-18.5) days after Labor Day (range, 15.5-20.3 days), in preschool children 19.4 (95% CI, 18.4-20.4) days after Labor Day (range, 17.3-22.2 days), and in adults 24.0 (95% CI, 22.4-25.6) days after Labor Day (range, 21.1-29.9 days).

The relation of the peak's timing in the 3 age groups and of Labor Day is shown in Fig 3. The timing of the calculated peaks was highly correlated to the timing of Labor Day in school-age children ($r = .77$; $P < .001$) and

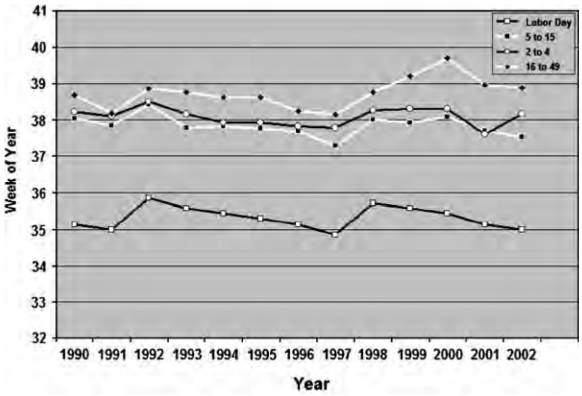

FIG 3. Calculated timing of the September epidemic peaks of asthma hospitalization by age group in relation to the timing of Labor Day from 1990 to 2002.

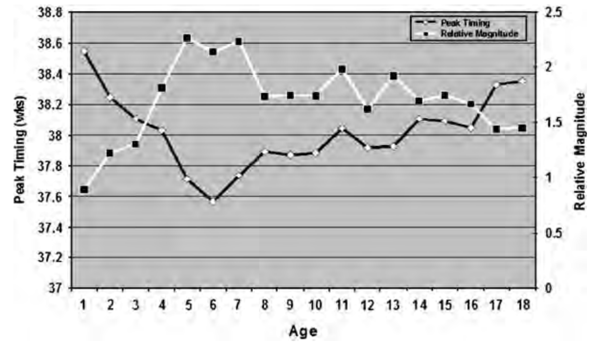

FIG 4. Calculated timing by week of the year in weeks from January 1 *(left y axis, black line)* and magnitude in multiples of the weekly mean *(right y axis, white line)* of the September epidemic peak by year of age using data aggregated across all study years.

preschool children ($r = .65$; $P < .01$) but less so in adults ($r = .49$; $P < .05$).

Differences in epidemic peak timing between age groups

The epidemic peaks for preschool children occurred later in every year but 1 (2001) than those of school-age children. The peaks in adults were later than in both child groups in every year. Over the period of 13 years, the average lag in the timing of the peak from school age to preschool children was 1.7 (95% CI, 0.9-2.5; $P < .01$) days and 6.3 days (95% CI, 4.7-7.9; $P < .001$) from school-age children to adults.

The timing of the peaks in school-age children was highly correlated to that in preschool children ($r = .74$; $P < .01$) but less so in adults ($r = .47$; $P = .05$).

Relative amplitude of the epidemic peaks in different age groups

Over the study period, the average amplitude of the epidemic peaks of asthma hospitalization, expressed as a multiple of the height of the background distribution in each respective age group, was 2.2 (95% CI, 1.9-2.6) for school-age children, 1.6 (95% CI, 1.3-1.9) for preschool children, and 1.0 (95% CI, 0.3-1.7) for adults, and was significantly larger in school-age children than in both preschool children ($P < .001$) and adults ($P < .01$).

Timing of the peaks of asthma epidemics in relation to latitude

In school-age children, there was a significant difference in the timing of the epidemic peak between ranges of latitude, with the delay of the peak from Labor Day increasing from 15.1 days for the northernmost (more than 52°), through 16.2 days for 51° and 52°, 17.7 days for 44° to 50°, to 19.2 days for the southernmost latitude (less than 44°). The mean difference between the northernmost and southernmost latitude ranges was 4.1 days (95% CI, 1.2-7.1 days; P < .01). There was no significant relationship with latitude in preschool children or adults. No significant differences were found in the amplitude of the peaks between latitudes for any age group.

Timing and magnitude of the peaks by age

We analyzed the timing and magnitude of the epidemic peaks in relation to individual year of age. The peak occurred earliest in 6-year-old children (Fig 4) and was progressively later with decreasing age down to 1 year and with increasing age to 18 years. From age 18 years to age 50 years, the timing of the peak remained constant (not shown). The magnitude of the peak was greatest in children between 5 and 7 years, increasing from ages 1 to 7 years, and declining from ages 7 to 18 years, from which it remained stable until age 50 years. Thus, children between 5 and 7 years old appear to be both the earliest and most seriously affected by the epidemics.

DISCUSSION

We have characterized a highly predictable epidemic of severe asthma exacerbations requiring hospitalization that occurs throughout Canada from north to south and have tracked the timing of Labor Day over a period of 13 years. The peak of the epidemic occurs first in school-age children, followed by preschool children and then adults.

This sequence suggests that agents provoking asthma exacerbations may be transferred during the September epidemic from school-age children to preschool children and adults with whom they are in contact. The magnitudes of the peaks were also greatest in school-age children, suggesting that their exposures were primary. The trends of peak timing and magnitude that occur between the ages 1 and 18 years (Fig 4) suggest that children age 5 to 7 years are primarily affected by the epidemic but that the risk is lower at earlier and later ages. This could be related to children 5 to 7 years old still being relatively naive in resistance to infectious agents. Aspects of their social behavior may also make them especially efficient at transmission of infectious agents.

The gradient we observed in timing and amplitude of the peaks from age 1 year to school attendance at age 5 years may reflect progressively greater exposure to other children in day care and preschool programs with age. In other words, if universal schooling occurred in Canada from age 2 years, there may have been no average difference between the groups 2 to 4 years old and 5 to 15 years old in peak timing or amplitude. At the midpoint of the study, it is estimated that 42% of all preschool children in Canada were cared for outside their homes. This proportion grew from 36% to 53% from 1988 to 2001 and continues to do so. These proportions were greater in older preschool children.[23]

Our finding that there was a gradient in the timing of the asthma exacerbation peak from north to south in school-age children is consistent with there being differences in conditions from north to south that may foster transmission of factors associated with asthma exacerbations. In northern Canada, fall days are colder than in the south. School catchment areas in the north are larger than in the south, and northern children may be in confined spaces such as school buses in the north for longer periods. It is also possible that both atmospheric and in-school allergen levels may vary quantitatively or qualitatively from north to south. The observation requires further investigation to determine its bases.

Rhinovirus infections are the predominant cause of respiratory infections in children in the early fall.[24] Between 80% and 85% of children with wheezing episodes test positive for respiratory viruses, predominantly rhinovirus, in both the emergency department[25,26] and community settings,[12] and half of exacerbations in adults with asthma are associated with rhinovirus infections.[24]

Peak periods for rhinovirus infection are reported to be quite distinct from the timing of influenza peaks.[27] They occur in the early fall, and to a lesser extent in the spring,[28,29] when the asthma hospitalization cycle also shows a rise, and have been demonstrated to begin in September a few days after school return.[29] Our finding that the peaks of asthma hospitalization tracked the timing of Labor Day over a period of 13 years supports the possibility that school return per se provides the conditions necessary to accelerate the transmission of rhinovirus infections to epidemic levels.

Canadian hospitalization data do not permit linkage to family data, and it is not possible to determine whether adults hospitalized for asthma in the early fall epidemic tend to have school-age children; however, the delays we have observed between the timing of peaks of asthma exacerbation in different age groups are consistent with school-age children being vectors of transmission of respiratory viral infections to adults and possibly younger siblings. It is possible that adults and children are exposed to factors precipitating the September epidemic simultaneously and that the differences observed between them in peak timing are biologically related to age; however, children have been shown in other studies to be primary introducers of respiratory tract infections to their families.[19,29,30]

Factors other than viral infections may contribute to asthma exacerbations after school return. Children may face substantial changes in allergen exposure on return to school. Cat allergen is transported to school by children on their clothing,[31] and fungal and pollen allergens may be more prevalent and at higher levels in schools than in homes.[32,33] It is feasible that allergen re-exposure and transfer from schools to homes may contribute to post school vacation asthma hospitalization peaks and that the effects observed in this study follow a combination of insults. This interpretation is made more likely by the demonstration that allergen exposure and virus infection have a synergistic interaction in increasing the risk of asthma exacerbation.[34]

Aeroallergens, air pollution, and their interactions with climate are important factors in the genesis of asthma exacerbations.[21] However, we believe that the sequence of peak timings and their relation to Labor Day that we have observed would be unlikely to occur if aeroallergen exposure was the primary cause of the September epidemic, because exposure of all age groups to these would be simultaneous.

We conclude that the September peak of asthma exacerbations has a highly predictable timing related directly to return to school return after Labor Day and that the source of this epidemic is school-age children, perhaps most notably those at the beginning of their schooling. Because viral infections, predominantly rhinovirus, have been previously shown to be associated with approximately 80% of asthma exacerbations in this age group,[11,12] and rhinovirus detections are most common at this time,[18,20] this study suggests that school-age children, particularly young school-age children, are vectors of transmission of the agents concerned to other family members.

Studies investigating prophylactic measures against respiratory virus infections could be profitably targeted to this age group in the late summer and early fall. The risks to patients with asthma during this period should be considered a priority by physicians engaged in their care.

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